FACILE SYNTHESIS OF 2-SUBSTITUTED 4H-1,3-THIAZINES AND 3-SUBSTITUTED 1,2-ISOTHIAZOLES VIA BENZYNIE INTERMEDIATES

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Abstract – Substituted 2-dialkylamino-4H-1,3-benzothiazines were synthesized by the reaction of (phenyl)[o-(trimethylsilyl)aryl]iodonium triflates and dialkyl-aminothiazadienes in the presence of 1.5 equivalent of Bu4NF. However, when these reactions were carried out in the presence of 4 equivalents of Bu4NF, 3-substituted 1,2-benzisothiazoles were obtained. Additionally, the reaction of phenyl[(3-trimethylsilyl)-2-naphthyl]iodonium triflate with dialkylaminothiazadienes in the presence of Bu4NF gave 3-substituted 1,2-naphthisothiazoles. A possible mechanism for the latter reaction involving the trapping of a benzyne intermediate with a nitrile sulfide generated in situ by the reaction of dialkylaminothiazadiene, fluoride ion and trimethylsilyl fluoride is proposed.

INTRODUCTION

Although 1,3-thiazines1-7 and isothiazoles8-10 show a wide range of biological activity, the synthetic and biological chemistry of 1,3-benzothiazine and benzisothiazole nuclei are relatively unexplored.11-14 Thus, there is much interest in developing efficient methods for their synthesis. In this regard, we recently
reported the preparation of a series of 4H-naphtho[2,3-e]-1,3-selenazines by the reaction of benzyynes with selenoazadienes. We also substituted the selenium atom in certain selenazines with sulfur and found that the resulting dialkylaminothiazadienes reacted with 2,3-naphthalyne to give 1,3-naphthothiazines. We have expanded this synthesis to the preparation of 4H-1,3-benzothiazines and report the results here. In addition, we report a novel synthesis of benzo- and naphthoisothiazoles, unexpectedly discovered during this work, and suggest a possible explanation for their formation.

RESULTS AND DISCUSSION

Synthesis of 2-Amino-4H-1,3-benzothiazines (4a-i). The required (phenyl)[o-trimethylsilylaryl]iodonium triflates (1a-d) were prepared from substituted dichlorobenzenes while the aminothiazadienes (3a-f) were on hand from a previous study. The generation of benzyynes (2a-d) were initially carried out by adding Bu4NF (1.5 equivalents) to a solution of the precursors (1a-d) at 0 °C in the presence of the dialkylaminothiazadienes. As shown in Scheme 1, the aminothiazadienes (3a–f) reacted with 2a–d to give 2-amino-4H-1,3-benzothiazines (4a–i) in 80-95% yields, which are shown in Table 1.

\[
\begin{align*}
\text{R}^1 & = \text{R}^2 = \text{R}^3 = \text{H}, \text{R}^4 = \text{OMe} \\
\text{b) R}^1 & = \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H} \\
\text{c) R}^1 & = \text{R}^2 = \text{H}, \text{R}^3 = \text{R}^4 = \text{OMe} \\
\text{d) R}^1 & = \text{R}^2 = \text{H}, \text{R}^3 = \text{R}^4 = \text{OMe} \\
\text{e) R}^1 & = \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}, \text{R}^5 = \text{R}^6 = \text{Et} \\
\text{f) R}^1 & = \text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}, \text{R}^5 = \text{R}^6 = \text{Me} \\
\text{g) R}^2 & = \text{R}^3 = \text{H}, \text{R}^1 = \text{R}^4 = \text{OMe}, \text{R}^5 = \text{R}^6 = \text{Me} \\
\text{h) R}^2 & = \text{R}^3 = \text{H}, \text{R}^1 = \text{R}^4 = \text{OMe}, \text{R}^5 + \text{R}^6 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2 \\
\text{i) R}^1 & = \text{R}^4 = \text{H}, \text{R}^2 = \text{R}^3 = \text{OMe}, \text{R}^5 + \text{R}^6 = \text{M}
\end{align*}
\]

Scheme 1

Compounds (4a–i) were identified on the basis of 1H NMR and 13C NMR spectroscopy. The structure of 2-(pyrrolidin-1-yl)-5-methoxy-4H-benzo[e][1,3]thiazine (4a) (entry 1) was also confirmed by X-Ray...
crystallographic analysis; an ORTEP drawing for 4a is shown in Figure 1. This unexpected product suggests that the aminothiazadiene (3a) added regioselectively to ultimately give 4a as shown in Figure 2. None of the 8-methoxy regioisomer was detected. The preferred addition of the sulfur atom in 3a to the 3-position of 1a is in accord with the strong meta directing effect of methoxy in aryne reactions.\textsuperscript{17} It

<table>
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<th>4</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>R\textsuperscript{3}</th>
<th>R\textsuperscript{4}</th>
<th>R\textsuperscript{5}</th>
<th>R\textsuperscript{6}</th>
<th>Yield, %</th>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
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<td>Me</td>
<td>89</td>
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**Figure 1** ORTEP of Compound (4a)
also indicates (as shown in Figure 2) that the formation of the powerfully nucleophilic sulfur atom of the thiocarbonyl group in 3a occurs ahead of that of the carbon of the C=N resulting in some charge build up and indicating that the [4+2] process is probably not completely concerted. A possible explanation for the preparation of 4a is shown in Scheme 2. Accordingly, the initial hetero-Diels-Alder reaction would give the adduct (5) which could afford the adduct (6) by a retro-ene reaction. A final 1,3-H shift would then give the more stable thiazine (4a). We are investigating the mechanism of these intriguing reactions.

Scheme 2

Synthesis of Benzisothiazoles.

During this investigation, we made another remarkable and unexpected discovery. When 4 equivalents of Bu₄NF was added to the reaction mixture of 1b and 3 rather than the previous 1.5 equivalents, under the same very mild conditions (DCM, 0 °C, 1 h), the reaction took an entirely different course. As shown in Scheme 3, instead of producing the benzothiazines (4), it gave the benzisothiazoles (7a–f) in high yields, which are shown in Table 2.

Scheme 3
Table 2. Preparation of Compounds (7a–f)

<table>
<thead>
<tr>
<th></th>
<th>Benzisothiazoles</th>
<th>Yield, %</th>
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<tr>
<td>a</td>
<td>R + R¹ = CH₂CH₂CH₂CH₂</td>
<td>90</td>
</tr>
<tr>
<td>b</td>
<td>R = R¹ = i-Pr</td>
<td>86</td>
</tr>
<tr>
<td>c</td>
<td>R + R¹ = CH₂CH₂OCH₂CH₂</td>
<td>94</td>
</tr>
<tr>
<td>d</td>
<td>R = R¹ = Et</td>
<td>93</td>
</tr>
<tr>
<td>e</td>
<td>R = R¹ = Me</td>
<td>91</td>
</tr>
<tr>
<td>f</td>
<td>R + R¹ = CH₂CH₂CH₂CH₂CH₂</td>
<td>85</td>
</tr>
</tbody>
</table>

Similarly, phenyl[3-trimethylsilyl-2-naphthyl]iodonium triflate (1e) reacted with 3a–f to give naphthisothiazoles (8a–f) in 81-96% yields (see Scheme 4). The results are given in Table 3.

Scheme 4

Table 3. Preparation of Compounds (8a–f)

<table>
<thead>
<tr>
<th></th>
<th>Naphthisothiazoles</th>
<th>Yield, %</th>
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<tbody>
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<td>a</td>
<td>R + R¹ = CH₂CH₂CH₂CH₂</td>
<td>82</td>
</tr>
<tr>
<td>b</td>
<td>R = R¹ = i-Pr</td>
<td>92</td>
</tr>
<tr>
<td>c</td>
<td>R + R¹ = CH₂CH₂OCH₂CH₂</td>
<td>94</td>
</tr>
<tr>
<td>d</td>
<td>R = R¹ = Et</td>
<td>88</td>
</tr>
<tr>
<td>e</td>
<td>R = R¹ = Me</td>
<td>81</td>
</tr>
<tr>
<td>f</td>
<td>R + R¹ = CH₂CH₂CH₂CH₂CH₂</td>
<td>96</td>
</tr>
</tbody>
</table>

The structures of 7 and 8 were determined by ¹H NMR and ¹³C NMR spectroscopy and in the case of 8f by X-Ray crystallography; an ORTEP of 8f is shown in Figure 3.

Our immediate thought was that the excess of Bu₄NF might be converting the 1,3-benzothiazines (4) into the benzisothiazoles (7). However, isothiazole (7a) was not detected after treating thiazine (4b) with 4 equivalents of Bu₄NF under the same conditions. Furthermore, Bu₄NF does not react with the
aminothiazadienes (3a) even after stirring at 45 °C overnight.

Figure 3 ORTEP of Compound (8f)

An explanation of the striking effect of Bu₄NF concentration on the reaction pathway could be as follows. As shown in Scheme 5, with the higher concentration of fluoride ion, and the resulting generation of
Me$_3$SiF (9) from 1b occurring more rapidly, there is a possibility of reaction between the dialkyl-
aminothiazadienes (3) with fluoride ion and Me$_3$SiF (9) to form an adduct (11). This could result in the
cleavage of 3 generating fluoro(dimethylamino)(trimethylsilyl)methane (13) and the thiazirine (12),
which rapidly rearranges to nitrile sulfide (15) and subsequently traps benzyne (2b) as it is formed from
the arene anion (10). With the lower concentration of Bu$_4$NF the rate of reaction of 3 with fluoride ion
and 9 will be reduced and the benzyne generated will be intercepted by the highly nucleophilic reactant
(3) acting as a Diels-Alder diene, as shown previously in Scheme 2.

Interestingly, substituted thiazirines like 12 have been proposed before, particularly as intermediates in
the extrusion of N$_2$, CO$_2$, etc. from 5-membered heterocyclic rings (e.g., 17 shown in Scheme 5), on their
way to nitrile sulfides. Furthermore, dimethylaminonitrile sulfide (15, R = Me) itself has been generated
by thermolysis of 5-dimethylamino-1,3,4-oxathiazol-2-one (17, R = Me) and trapped by cycloaddition to
an electron-deficient cyanide.

In summary, a novel approach to substituted 2-amino-4H-1,3-benzothiazines and 3-aminobenzoiso-
thiazoles was successfully achieved by a direct one-pot reaction of (phenyl)[o-trimethylsilylaryl]-
iodonium triflates with aminothiazadienes. The 1,3-benzothiazines were obtained in high yields when 1.5
equivalents of Bu$_4$NF was used. However, the isothiazoles were obtained in excellent yields when the
reactions were carried out with 4 equivalents of Bu$_4$NF; if our mechanism is correct, this is, to the best of
our knowledge, the first reported cycloaddition of a nitrile sulfide to a benzyne.

**EXPERIMENTAL**

**General Data.** Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected with
respect to stem exposure. $^1$H NMR and $^{13}$C NMR spectra were recorded on a 400 MHz Bruker AVANCE
DRX-400 Multi-nuclear NMR spectrometer. Chemical shifts are reported in reference to TMS as internal
standard. Elemental analyses were carried out in the SMU Analytical Laboratory. The glassware was
heated overnight in an oven at 125 °C prior to use. All the reactions were done under an atmosphere of
dry O$_2$–free Ar via balloon. Column chromatography refers to flash chromatography performed on Merck
silica gel 60, 230–400 mesh.

**General Procedure for the Synthesis of 2-Substituted 4H-Benzof1,3]thiazines (4a–f).** A solution of
Bu$_4$NF in THF (0.84 mL of a 1 M solution) was added to a solution containing the aryne precursor (1a-d)
(0.56 mmol), and the aminothiazadiene (3a–f) (0.84 mmol) in CH$_2$Cl$_2$ (15 mL) at 0 °C and stirred at this
temperature for 1 h. The reaction mixture was then quenched with H$_2$O and the resulting mixture was
extracted with 3 X 20 mL portions of CH$_2$Cl$_2$. The combined extracts were dried (Na$_2$SO$_4$) and evaporated
under reduced pressure. The crude product was then purified by column chromatography using
hexanes–ethyl acetate mixtures (9:1 to 5:5, respectively) as eluents. The physical and spectral properties
of 4a–f are shown below.

2-(Pyrrolidin-1-yl)-5-methoxy-4H-benzo[e][1,3]thiazine (4a) was obtained as a colorless solid, mp 142 °C (CHCl₃/hexanes) in 94% yield (132 mg). ¹H NMR (400 MHz, CDCl₃) δ 1.76 (4H, m, 2xCH₂), 3.54 (4H, m, CH₂NCH₂), 3.84 (3H, s, 5-OCH₃), 4.51 (2H, s, 4-CH₂), 6.41 (1H, d, J = 8 Hz, 6-H), 6.92 (1H, d, J = 7 Hz, 7-H), 7.17–7.20 (1H, m, 8-H). ¹³C NMR (100 MHz, CDCl₃) δ 25.3 (2 x CH₂), 49.5 (CH₂NCH₂), 53.8 (CH₂ C₄), 56.1 (5-OCH₃), 125.1 (C₄a), 126.3 (C₅), 128.7 (C₆), 131.3 (C₇), 134.2 (C₈), 155.6 (C₈a), 156.8 (C₉). Anal. Calcd for C₁₃H₁₆N₂OS: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.84; H, 6.42; N, 11.23.

2-(Pyrrolidin-1-yl)-4H-benzo[e][1,3]thiazine (4b) was obtained as a colorless solid, mp 120 °C (CHCl₃/hexanes), in 91% yield (124 mg). ¹H NMR (400 MHz, CDCl₃) δ 1.93 (4H, m, 2 x CH₂), 3.52–3.56 (4H, m, CH₂NCH₂), 4.55 (2H, s, 4-CH₂), 7.41 (2H, m, 5-H, 8-H), 7.86–7.89 (2H, m, 6-H, 7-H). ¹³C NMR (100 MHz, CDCl₃) δ 25.7 (2 x CH₂), 46.3 (-NCH₂), 48.8 (-NCH₂), 52.4 (CH₂ C₄), 109.5 (C₄a), 119.7 (C₅), 123.6 (C₆), 127.8 (C₇), 133.2 (C₈), 154.8 (C₈a), 156.4 (C₉). Anal. Calcd for C₁₂H₁₄N₂S: C, 66.02; H, 6.46; N, 12.83. Found: C, 66.15; H, 6.51; N, 12.87.

2-Diisopropylamino-4H-benzo[e][1,3]thiazine (4c) was obtained as a light brown solid, mp 134 °C (CHCl₃/hexanes), in 83% yield (145 mg). ¹H NMR (400 MHz, CDCl₃) δ 1.33 (12H, t, J = 5 Hz, 4 x CH₃), 4.05 (2 H, m, 2 x NCH), 4.21 (2H, m, 2 x NCH), 7.45–7.48 (2H, m, 5-H, 8-H), 7.85 (2H, m, 6-H, 7-H). ¹³C NMR (100 MHz, CDCl₃) δ 21.5 (2 x CH₃), 22.7 (2 x CH₃), 48.4 (NCH), 51.2 (NCH), 53.5 (CH₂ C₄), 121.5 (C₄a), 122.3 (C₅), 124.7 (C₆), 125.3 (C₇), 133.2 (C₈), 154.1 (C₈a), 159.3 (C₉). Anal. Calcd for C₁₄H₂₀N₂S: C, 67.70; H, 8.12; N, 11.28. Found: C, 67.66; H, 8.05; N, 11.19.

2-(Morpholin-4-yl)-4H-benzo[e][1,3]thiazine (4d) was obtained as a colorless solid, mp 128 °C (CHCl₃/hexanes), in 89% yield (250 mg). ¹H NMR (400 MHz, CDCl₃) δ 3.56–3.60 (4H, m, CH₂OCH₂), 3.71 (4H, m, CH₂NCH₂), 4.15 (2H, s, 4-CH₂), 7.50 (2H, m, 5-H, 8-H), 7.85 (2H, m, 6-H, 7-H). ¹³C NMR (100 MHz, CDCl₃) δ 47.2 (CH₂OCH₂), 52.7 (CH₂NCH₂), 66.8 (CH₂ C₄), 122.5 (C₄a), 125.0 (C₅), 125.6 (C₆), 127.9 (C₇), 128.4 (C₈), 151.7 (C₈a), 163.3 (C₉). Anal. Calcd for C₁₂H₁₄N₂OS: C, 61.51; H, 6.02; N, 11.96. Found: C, 61.57; H, 6.09; N, 11.91.

2-Diethylamino-4H-benzo[e][1,3]thiazine (4e) was obtained as a colorless liquid in 94% yield (135 mg). ¹H NMR (400 MHz, CDCl₃) δ 1.28 (6 H, t, J = 6 Hz, 2 x CH₃), 3.57 (4H, q, J = 6.0 Hz, 2 x CH₃), 4.31 (2H, s, 4-CH₂), 7.25 (2H, m, 5-H, 8-H), 7.45–7.49 (2H, m, 6-H, 7-H). ¹³C NMR (100 MHz, CDCl₃) δ 13.91 (2 x CH₃), 43.3 (CH₂NCH₂), 56.6 (CH₂ C₄), 125.4 (C₄a), 125.4 (C₅), 126.9 (C₆), 127.7 (C₇), 132.1 (C₈), 135.4 (C₈a), 158.2 (C₉). Anal. Calcd for C₁₂H₁₄N₂S: C, 65.41; H, 7.32; N, 12.71. Found: C, 65.38; H, 7.36; N, 12.69.

2-Dimethylamino-4H-benzo[e][1,3]thiazine (4f) was obtained as a brown solid, mp 74–76 °C (CHCl₃/hexanes), in 80% yield (118 mg). ¹H NMR (400 MHz, CDCl₃) δ 3.18 (6H, s, CH₃NCH₃), 4.23
(2H, s, 4-CH$_2$), 7.39 (2H, dd $J = 6.3$ Hz, 3.1 Hz, 5-H, 8-H), 7.85–7.89 (2H, m, 6-H, 7-H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 41.2 (CH$_3$NCH$_3$), 57.2 (CH$_2$ C$_4$), 122.6 (C$_{4a}$), 125.1 (C$_5$), 125.9 (C$_6$), 127.5 (C$_7$), 128.2 (C$_8$), 138.3 (C$_{8a}$), 159.4 (C$_2$). Anal. Calcd for C$_{10}$H$_{12}$N$_2$S: C, 62.46; H, 6.29; N, 14.57. Found: C, 62.47; H, 6.32; N, 14.59.

2-Dimethylamino-5, 8-dimethoxy-4H-benzo[e1,3]thiazine (4g) was obtained as a light red liquid in 95% yield (126 mg). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.28 (6H, s, CH$_3$NCH$_3$), 3.77 (3H, s, 5-OCH$_3$), 3.45 (3H, s, 8-OCH$_3$), 4.50 (2H, s, 4-CH$_2$), 6.69 (1H, d, $J = 8.0$ Hz, 6-H), 6.82 (1H, d, $J = 8.0$ Hz, 7-H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 41.3 (CH$_3$NCH$_3$), 54.2 (5-OCH$_3$), 55.5 (8-OCH$_3$), 62.2 (CH$_2$ C$_4$), 109.4 (C$_{4a}$), 110.1 (C$_5$), 118.8 (C$_6$), 123.6 (C$_7$), 148.8 (C$_8$), 150.3 (C$_{8a}$), 155.2 (C$_2$). Anal. Calcd for C$_{12}$H$_{16}$N$_2$O$_2$S: C, 57.12; H, 6.39; N, 11.10. Found: C, 57.09; H, 6.33; N, 11.07.

2-(Pyrrolidin-1-yl)-5,8-dimethoxy-4H-benzo[e1,3]thiazine (4h) was obtained as a colorless solid, mp 126–127 °C (CHCl$_3$/hexanes), in 91% yield (106 mg). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.94 (4 H, m, 2 x CH$_2$), 3.48–3.51 (4 H, m, CH$_2$NCH$_2$), 3.79 (3 H, s, 5-OCH$_3$), 3.83 (3H, s, 8-OCH$_3$), 4.47 (2 H, s, 4-CH$_2$), 6.73 (1 H, d, $J = 8$ Hz, 6-H), 6.81 (1 H, d, $J = 8$ Hz, 7-H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 25.1 (2 x CH$_2$), 48.5 (-NCH$_2$), 48.9 (NCH$_2$), 57.1 (5-OCH$_3$), 57.2 (8-OCH$_3$), 64.8 (CH$_2$ C$_4$), 109.4 (C$_{4a}$), 110.2 (C$_5$), 118.4 (C$_6$), 125.6 (C$_7$), 149.7 (C$_8$), 152.2 (C$_{8a}$), 154.8 (C$_2$). Anal. Calcd for C$_{14}$H$_{18}$N$_2$O$_2$S: C, 60.41; H, 6.52; N, 10.06. Found: C, 60.45; H, 6.47; N, 11.11.

6, 7-Dimethoxy-2-dimethylamino-4H-benzo[e1,3]thiazine (4i) was obtained as colorless solid, mp 135°C (CHCl$_3$/hexanes), in 89% yield (129 mg). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.58 (6H, s, CH$_3$NCH$_3$), 3.67 (3H, s, 6-OCH$_3$), 3.72 (3H, s, 7-OCH$_3$), 4.53 (2H, s, 4-CH$_2$), 7.22 (1H, s, 5-H), 7.34 (1H, s, 8-H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 40.6 (CH$_3$NCH$_3$), 54.8 (6-OCH$_3$), 55.4 (7-OCH$_3$), 61.7 (CH$_2$ C$_4$), 110.1 (C$_{4a}$), 111.4 (C$_5$), 119.7 (C$_6$), 124.9 (C$_7$), 147.9 (C$_8$), 151.3 (C$_{8a}$), 156.2 (C$_2$). Anal. Calcd for C$_{12}$H$_{16}$N$_2$O$_2$S: C, 57.12; H, 6.39; N, 11.10. Found: C, 57.09; H, 6.37; N, 11.06.

General Procedure for the Preparation of 3-Substituted 1,2-Benzisothiazoles (7a-f). To a solution of 1 (0.59 mmol) and 3 (0.84 mmol) in CH$_2$Cl$_2$ (15 mL) was added a THF solution of Bu$_4$NF (1M, 2.39 mL) at 0 °C. After 1 h of stirring at 0 °C, 40 mL of water was added and the resulting medium was allowed to warm to rt. After extraction with CH$_2$Cl$_2$ and washing with water, the combined organic phases were dried (Na$_2$SO$_4$) and evaporated under reduced pressure. The crude product was then purified by column chromatography on silica gel using hexane–ethyl acetate (9:1 to 5:5, respectively) mixtures as eluents.

The physical and spectral properties of 7a-f are shown below.

3-(Pyrrolidin-1-yl)-1,2-benzisothiazole (7a) was obtained as a colorless solid, mp 50°C(CHCl$_3$/hexanes), (lit.,$^{20}$ mp 49-50 °C) in 90% yield (111 mg). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.86 (4 H, m, 2 x CH$_2$), 3.61
(4 H, m, CH₂NCH₂), 7.31 (1 H, d, J = 7.0 Hz, H-5), 7.42 (1 H, d, J = 7.0 Hz, H-6), 7.75 (1 H, t, J = 6.8 Hz, H-7), 7.89 (1H, t, J = 6.7 Hz, H-4). ¹³C NMR (100 MHz, CDCl₃) δ 26.5, 49.2, 121.2, 124.5, 125.1, 126.3, 128.5, 130.4, 164.8.

3-Diisopropylamino-1,2-benzisothazole (7b) was obtained as a light brown solid, mp 89 °C (CHCl₃/hexanes), in 86 % yield (186 mg). ¹H NMR (400 MHz, CDCl₃) δ 1.34 (12H, t, J = 5.0 Hz, 4 x CH₃), 3.99 (2H, m, 2 x CH), 7.33 (1H, t, J = 7.4 Hz, H-5), 7.43 (1H, t, J = 7.5 Hz, H-6), 7.82 (1H, d, J = 8.0 Hz, H-7), 7.95 (1H, d, J = 8.0 Hz, H-4). ¹³C NMR (100 MHz, CDCl₃) δ 22.4, 50.1, 120.6, 124.0, 124.9, 127.4, 132.1, 152.3, 163.4. Anal. Calcd for C₁₃H₁₈N₂S: C, 66.62; H, 7.74; N, 11.95. Found: C, 66.58; H, 7.62; N, 11.84.

3-(Morpholin-4-yl)-1,2-benzisothazole (7c) was obtained as colorless solid, mp 53 °C (CHCl₃/hexanes) (lit., 21 mp 52-53 °C), in 94% yield (146 mg). ¹H NMR (400 MHz, CDCl₃) δ 3.56 (4H, t, J = 4.7 Hz, CH₂-NCH₂), 3.95 (4H, t, J = 4.6 Hz, CH₂-O-CH₂), 7.38 (1H, t, J = 7.3 Hz, H-5), 7.50 (1H, t, J = 7.3 Hz, H-6), 7.85 (1H, d, J = 8.1 Hz, H-7), 7.92 (1H, d, J = 8.1 Hz, H-4); ¹³C NMR (100 MHz, CDCl₃) δ 51.0, 67.1, 121.0, 124.1, 124.3, 128.0, 128.2, 153.3, 164.2.

3-Diethylamino-1,2-benzisothiazole (7d) was obtained as a colorless viscous oil (reported 22 as a solid with mp 95-115 °C) in 93% yield (152 mg). ¹H NMR (400 MHz, CDCl₃) δ 1.31 (6H, t, J = 7.0 Hz, 2 x CH₃), 3.64 (4H, q, J = 7.0 Hz, 2 x CH₂), 7.34 (1H, t, J = 7.8 Hz, H-5), 7.45 (1H, d, J = 7.6 Hz, H-6), 7.79 (1H, d, J = 8.0 Hz, H-7), 7.96 (1H, d, J = 8.1 Hz, H-4); ¹³C NMR (100 MHz, CDCl₃) δ 13.8, 45.6, 120.8, 124.0, 124.6, 127.5, 128.3, 153.3, 162.5. ¹H NMR (400 MHz, CDCl₃) δ 1.82 (6H, br s, 3 x CH₂), 3.49 (4H, br s, CH₂NCH₂), 25.0, 26.3, 51.8, 120.8, 124.1, 124.4, 127.7, 127.8, 129.2, 152.4, 165.3. Anal. Calcd for C₁₂H₁₄N₂S: C, 60.64; H, 6.46; N, 15.72. Found: C, 60.73; H, 5.72; N, 15.83.

3-Dimethylamino-1,2-benzisothiazole (7e) was obtained as a colorless solid, mp 94 °C (CHCl₃/hexanes), in 91% yield (185 mg). ¹H NMR (400 MHz, CDCl₃) δ 3.23 (6H, br s, CH₃NCH₃), 7.35 (1H, t, J = 7.7 Hz, H-5), 7.46 (1H, t, J = 7.3 Hz, H-6), 7.80 (1H, d, J = 8.0 Hz, H-7), 8.05 (1H, d, J = 8.1 Hz, H-4); ¹³C NMR (100 MHz, CDCl₃) δ 42.2, 120.8, 124.0, 124.8, 127.7, 128.2, 153.4, 164.4. Anal. Calcd for C₉H₁₀N₂S: C, 60.64; H, 5.65; N, 15.72. Found: C, 60.73; H, 5.72; N, 15.83.

3-(Piperidin-1-yl)-1,2-benzisothiazole (7f) was obtained as a colorless liquid, in 85% yield (128 mg). ¹H NMR (400 MHz, CDCl₃) δ 1.82 (6H, br s, 3 x CH₂), 3.49 (4H, br s, CH₂NCH₂), 7.36 (1H, d, J = 7.1 Hz, H-5), 7.45 (1H, d, J = 7.0 Hz, H-6), 7.81 (1H, t, J = 6.7 Hz, H-7), 7.92 (1H, t, J = 6.5 Hz, H-4); ¹³C NMR (100 MHz, CDCl₃) δ 25.0, 26.3, 51.8, 120.8, 124.1, 124.4, 127.7, 128.7, 129.2, 152.4, 165.3. Anal. Calcd for C₁₂H₁₄N₂S: C, 66.02; H, 6.46; N, 12.03. Found: C, 66.14; H, 6.35; N, 12.12.

**General Procedure for the Synthesis of 3-Pyrrolidin-2-yl-1,2-naphthoisothiazoles (8a–f).** These compounds were similarly prepared as described for the synthesis of 7a-f with the exception that phenyl-
3-trimethylsilyl-2-naphthyliodonium triflate (1e) (300 mg, 0.54 mmol), 3 (0.82 mmol), and tetrabutylammonium fluoride (1M, 2.17 mL) were used. The physical and spectral properties of 8a–f are shown below.

3-(Pyrrolidin-1-yl)-1,2-naphthisothiazole (8a) was obtained as a colorless solid, mp 135 °C (CHCl3/hexanes), in 82% yield (195 mg). 1H NMR (400 MHz, CDCl3) δ 1.92 (4H, m, 2 x CH2), 3.59 (4H, m, CH2NCH2), 7.53 (1H, t, J = 7.0 Hz, H-7), 7.59 (1H, t, J = 7.0 Hz, H-6), 7.95 (1H, d, J = 8.4 Hz, H-8), 8.03 (1H, d, J = 8.3 Hz, H-5), 8.21 (1H, s, H-9), 8.37 (1H, s, H-4); 13C NMR (100 MHz, CDCl3) δ 26.1, 49.4, 120.2, 123.5, 124.1, 126.4, 127.5, 128.7, 129.6, 130.1, 131.8, 149.0, 163.7. Anal. Calcd for C15H14N2S: C, 70.83; H, 5.55; N, 11.01. Found: C, 70.76; H, 5.47; N, 11.09.

3-Diisopropylamino-1,2-naphthoisothiazole (8b) was obtained as a light brown solid, mp 78 °C (CHCl3/hexanes), in 92% yield (150 mg). 1H NMR (400 MHz, CDCl3) δ 1.41 (12H, t, J = 5.1 Hz, 4 x CH3), 4.12 (2H, m, 2 x CH), 7.49 (1H, t, J = 7.3 Hz, H-7), 7.56 (1H, t, J =7.4 Hz, H-6), 7.92 (1H, d, J = 8.0 Hz, H-5), 8.01 (1H, d, J = 8.0 Hz, H-5), 8.25 (1H, s, H-9), 8.49 (1H, s, H-4); 13C NMR (100 MHz, CDCl3) δ 22.5, 50.1, 118.0, 124.3, 125.4, 127.5, 129.8, 130.2, 130.6, 131.8, 132.8, 147.5, 162.9. Anal. Calcd for C17H20N2S: C, 71.79; H, 7.09; N, 9.85. Found: C, 71.84; H, 7.15; N, 9.76.

3-(Morpholin-4-yl)-1,2-naphthoisothiazole (8c) was obtained as colorless crystals, mp 120 °C (CHCl3/hexanes), in 94% yield (148 mg). 1H NMR (400 MHz, CDCl3) δ 3.66 (4H, t, J = 4.8 Hz, CH2N-CH2), 4.02 (4H, t, J = 4.7 Hz, CH2-O-CH2), 7.52 (1H, t, J = 7.8 Hz, H-7), 7.59 (1H, t, J = 7.9 Hz, H-6), 7.94 (1H, d, J = 8.1 Hz, H-8), 8.03 (1H, d, J = 8.2 Hz, H-5), 8.28 (1H, s, H-9), 8.46 (1H, s, H-4); 13C NMR (100 MHz, CDCl3) δ 51.0, 67.2, 118.6, 123.7, 125.9, 127.7, 127.9, 129.5, 130.6, 133.0, 148.1, 163.8. Anal. Calcd for C15H14N2OS: C, 66.64; H, 5.22; N, 10.36. Found: C, 66.72; H, 5.29; N, 10.43.

3-Diethylamino-1,2-naphthoisothiazole (8d) was obtained as a colorless liquid in 88% yield (95 mg). 1H NMR (400 MHz, CDCl3) δ 1.38 (6H, t, J = 7.0 Hz, 2 x CH3), 3.74 (4H, q, J = 7.0 Hz, CH2N-CH2), 7.49 (1H, t, J = 7.9 Hz, H-7), 7.57 (1H, t, J = 7.8 Hz, H-6), 7.91 (1H, d, J = 8.3 Hz, H-8), 8.01 (1H, d, J = 8.2 Hz, H-5), 8.23 (1H, s, H-9), 8.51 (1H, s, H-4); 13C NMR (100 MHz, CDCl3) δ 13.8, 45.7, 118.1, 124.2, 125.5, 127.5, 128.4, 129.8, 130.5, 132.7, 148.4, 162.1. Anal. Calcd for C15H16N2S: C, 70.27; H, 6.29; N, 10.93. Found: C, 70.16; H, 6.18; N, 10.86.

3-Dimethylamino-1,2-naphthoisothiazole (8e) was obtained as a colorless solid, mp 94 °C (CHCl3/hexanes), in 81% yield (185 mg). 1H NMR (400 MHz, CDCl3) δ 3.34 (6H, s, CH3NCH3), 7.51 (1H, t, J = 7.7 Hz, H-7), 7.58 (1H, t, J = 7.6 Hz, H-6), 7.92 (1H, d, J = 8.3 Hz, H-8), 8.02 (1H, d, J = 8.1 Hz, H-5), 8.23 (1H, s, H-9), 8.61 (1H, s, H-4); 13C NMR (100 MHz, CDCl3) δ 42.4, 118.3, 124.8, 125.7, 126.4, 127.5, 128.0, 128.9, 129.2, 130.2, 151.2, 166.7. Anal. Calcd for C13H12N2S: C, 68.39; H, 5.30; N, 12.27.
3-(Piperdin-1-yl)-1,2-naphthoisothiazole (8f) was obtained as colorless crystals, mp 121°C (CHCl₃/hexanes), in yield of 96% (174 mg). ¹H NMR (400 MHz, CDCl₃) δ 1.58 (6H, br s, 3 x CH₂), 3.60 (4H, br s, CH₂NCH₂), 7.51 (1H, t, J = 7.0 Hz, H-7), 7.58 (1H, t, J = 7.0 Hz, H-6), 7.93 (1H, d, J = 8.3 Hz, H-8), 8.03 (1H, d, J = 8.2 Hz, H-5), 8.25 (1H, s, H-9), 8.46 (1H, s, H-4); ¹³C NMR (100 MHz, CDCl₃) δ 25.1, 26.3, 51.9, 118.3, 124.0, 125.6, 127.6, 127.7, 128.4, 129.6, 130.5, 132.9, 148.0, 164.9. Anal. Calcd for C₁₆H₁₆N₂S: C, 71.61; H, 6.01; N, 10.44. Found: C, 71.54; H, 5.87; N, 10.36.

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