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FACILE SYNTHESIS OF 2-SUBSTITUTED 4*H*-1,3-THIAZINES AND 3-SUBSTITUTED 1,2-ISO-THIAZOLES *VIA* BENZYNE INTERMEDIATES

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Abstract – Substituted 2-dialkylamino-4*H*-1,3-benzothiazines were Synthesizedby the reaction of (phenyl)[o-(trimethylsilyl)aryl]iodonium triflates and dialkyl-aminothiazadienes in the presence of 1.5 equivalent of Bu_4NF. However, when these reactions were carried out in the presence of 4equivalents of Bu_4NF, 3-substituted 1,2-benzisothiazoles were obtained. Additionally, the reaction of phenyl[(3-trimethylsilyl)-2-naphthyl]iodo-nium triflate with dialkylaminothia-zadienes in the presence of Bu_4NF gave 3-substituted 1,2-naphthisothiazoles. A possible mechaism 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.

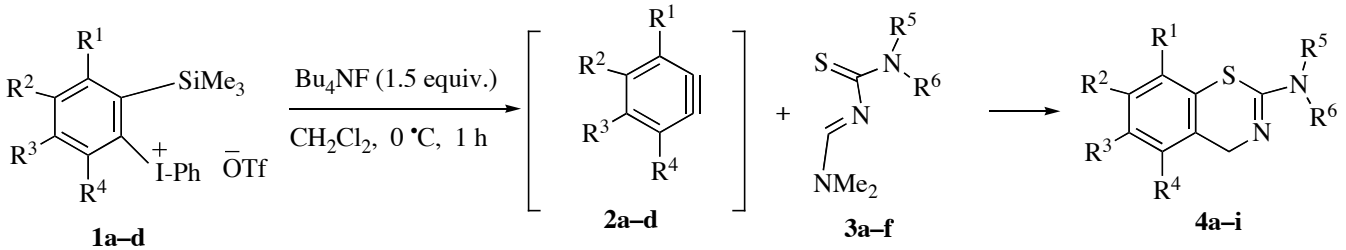
INTRODUCTION

Although 1,3-thiazines[1–7] and isothiazoles[8–10] 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 4*H*-naphtho[2,3-*e*]-1,3-selenazines by the reaction of benzynes with selenoazadienes.[15] 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.[15] We have expanded this synthesis to the preparation of 4*H*-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-4*H*-1,3-benzothiazines (4a-i). The required (phenyl)[o-trimethylsilyl-aryl]iodonium triflates (**1a-d**) were prepared from substituted dichlorobenzenes[16] while the aminothiazadienes (**3a-f**) were on hand from a previous study.[15] The generation of benzynes (**2a-d**) were initially carried out by adding Bu_4NF (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-4*H*-1,3-benzothiazenes (**4a-i**) in 80-95% yields, which are shown in Table 1**.**



1a–d **2a–d** **3a–f** **4a–i**

a) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$

b) $R^1 = R^2 = R^3 = R^4 = H$

c) $R^1 = R^4 = H$, $R^2 = R^3 = OMe$

d) $R^1 = R^4 = H$, $R^2 = R^3 = OMe$

a) $R^1 = R^2 = R^3 = H$, $R^4 = OMe$, $R^5 + R^6 = CH_2CH_2CH_2CH_2$

b) $R^1 = R^2 = R^3 = R^4 = H$, $R^5 + R^6 = CH_2CH_2CH_2CH_2$

c) $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = R^6 = i$-Pr

d) $R^1 = R^2 = R^3 = R^4 = H$, $R^5 + R^6 = CH_2CH_2\,OCH_2CH_2$

e) $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = R^6 = Et$

f) $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = R^6 = Me$

g) $R^2 = R^3 = H$, $R^1 = R^4 = OMe$, $R^5 = R^6 = Me$

h) $R^2 = R^3 = H$, $R^1 = R^4 = OMe$, $R^5 + R^6 = CH_2CH_2CH_2CH_2$

i) $R^1 = R^4 = H$, $R^2 = R^3 = OMe$, $R^5 + R^6 = M$

Scheme 1

Compounds (**4a–i**) were identified on the basis of ^1H NMR and ^{13}C NMR spectroscopy. The structure of 2-(pyrrolidin-1-yl)-5-methoxy-4*H*-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

Table 1. Preparation of **4a-i**

entry	**4**	R^1	R^2	R^3	R^4	R^5	R^6	Yield, %
1	**a**	H	H	H	OMe	$CH_2CH_2CH_2CH_2$		94
2	**b**	H	H	H	H	$CH_2CH_2CH_2CH_2$		91
3	**c**	H	H	H	H	*i*-Pr	*i*-Pr	83
4	**d**	H	H	H	H	$CH_2CH_2OCH_2CH_2$		89
5	**e**	H	H	H	H	Et	Et	94
6	**f**	H	H	H	H	Me	Me	80
7	**g**	OMe	H	H	OMe	Me	Me	95
8	**h**	OMe	H	H	OMe	$CH_2CH_2CH_2CH_2$		91
9	**i**	H	OMe	OMe	H	Me	Me	89

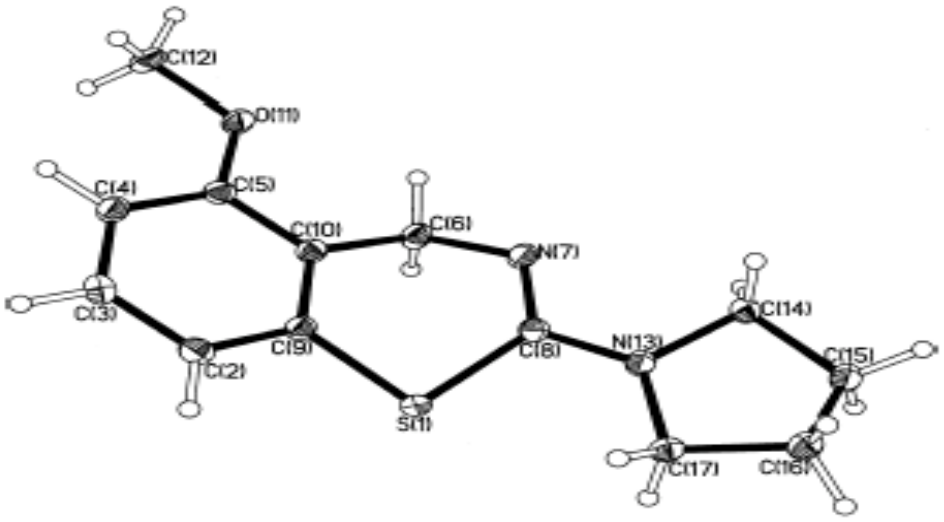


Figure 1 ORTEP of Compound (**4a**)

1 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.[17] It

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

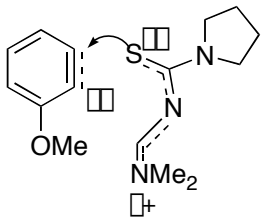
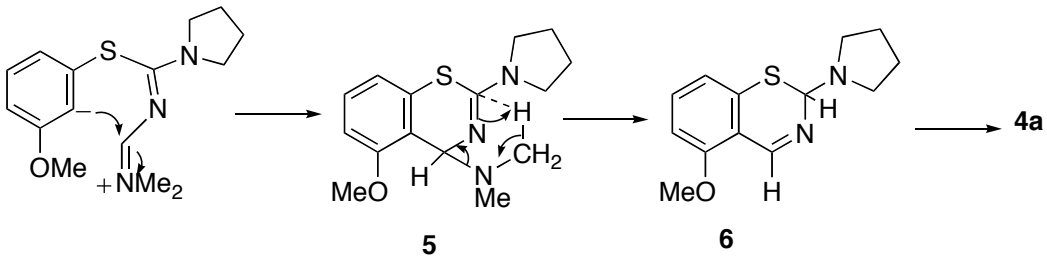


Figure 2 A possible transition state for the cycloaddition of **2a** and aminothiazadiene (**3a**)

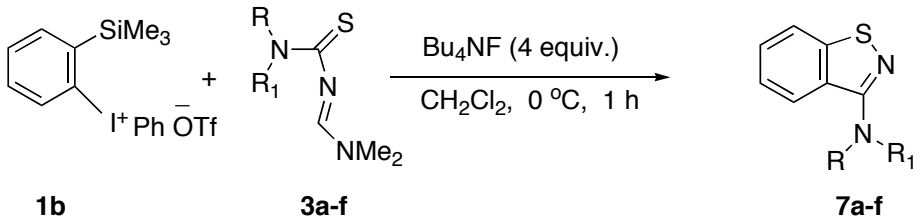
build up and indicating that the [4+2] process is probably not completely concerted. A possible explanation for the preparation of **4a** is shown in Scheme 2. Accordingly, the initial hetero-Diels-Alder reaction would give the adduct (**5**) which could afford the adduct (**6**) by a retro-ene reaction. 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 Bu_4NF 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.

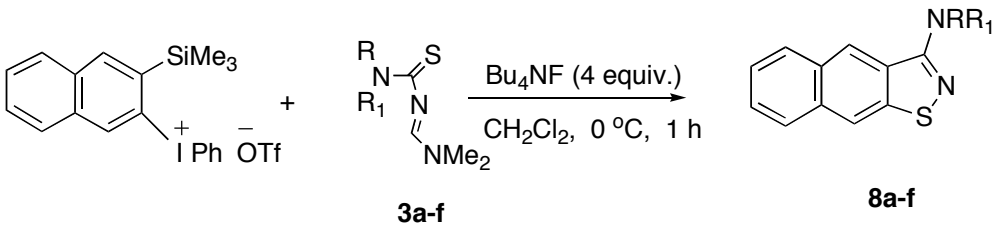


Scheme 3

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

7	Benzisothiazoles	Yield, %
a	$R + R^1 = CH_2CH_2CH_2CH_2$	90
b	$R = R^1 = i$-Pr	86
c	$R + R^1 = CH_2CH_2\ OCH_2CH_2$	94
d	$R = R^1 = Et$	93
e	$R = R^1 = Me$	91
f	$R + R^1 = CH_2CH_2CH_2CH_2CH_2$	85

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.



3a-f **8a-f**

Scheme 4

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

8	Naphthisothiazoles	Yield, %
a	$R + R^1 = CH_2CH_2CH_2CH_2$	82
b	$R = R^1 = i$-Pr	92
c	$R + R^1 = CH_2CH_2OCH_2CH_2$	94
d	$R = R^1 = Et$	88
e	$R = R^1 = Me$	81
f	$R + R^1 = CH_2CH_2CH_2CH_2CH_2$	96

The structures of **7** and **8** were determined by ^{1}H NMR and ^{13}C 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 Bu_4NF 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 Bu_4NF under the same conditions. Furthermore, Bu_4NF does not react with the

aminothiazadienes (**3a**) even after stirring at 45 °C overnight.

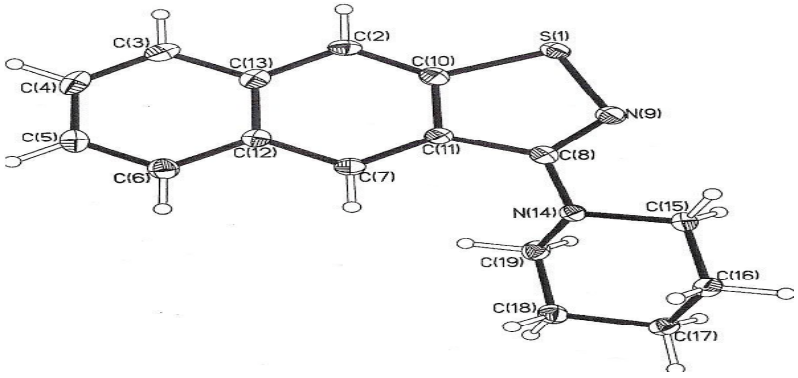
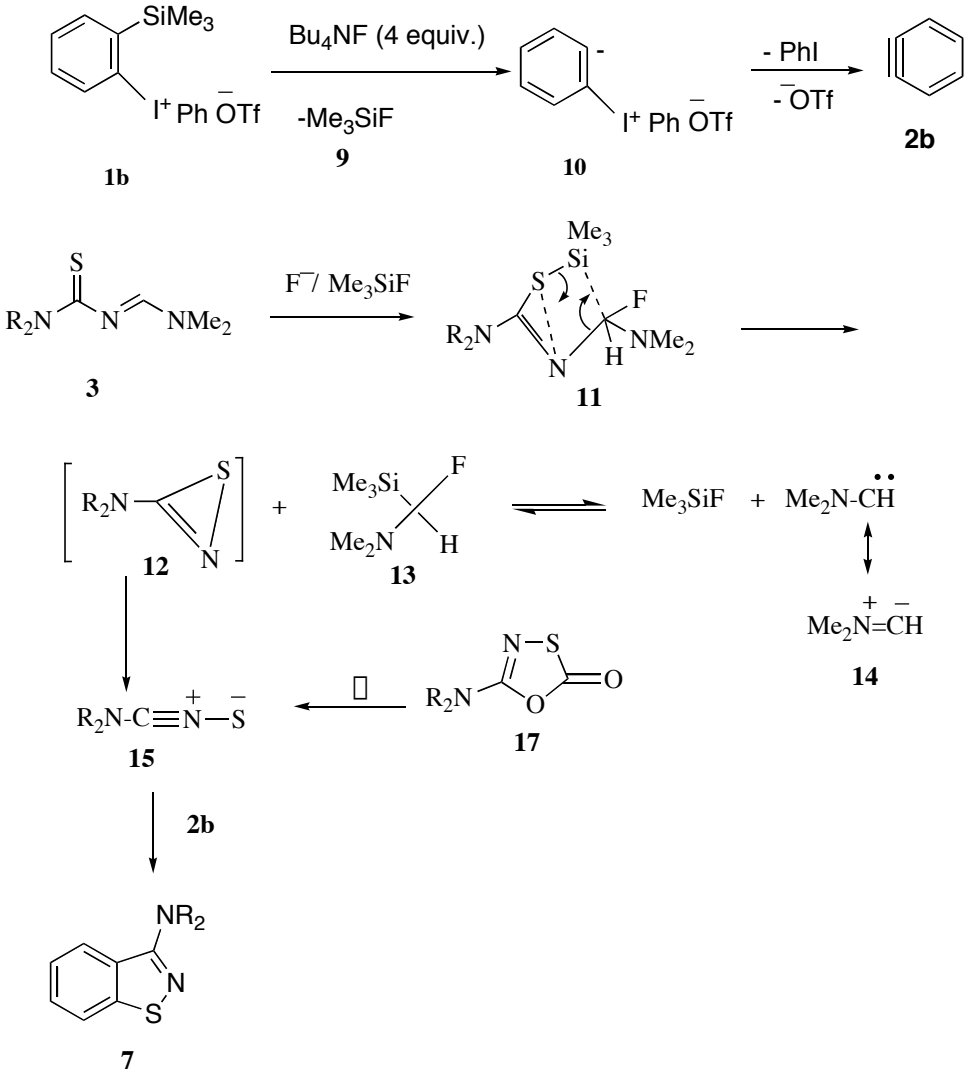


Figure 3 ORTEP of Compound (**8f**)

An explanation of the striking effect of Bu_4NF 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



Scheme 5

Me_3SiF (**9**) from **1b** occurring more rapidly, there is a possibility of reaction between the dialkylaminothiazadienes (**3**) with fluoride ion and Me_3SiF (**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_4NF 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.[18] 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.[19]

In summary, a novel approach to substituted 2-amino-4*H*-1,3-benzothiazines and 3-aminobenzoisothiazoles 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_4NF was used. However, the isothiazoles were obtained in excellent yields when the reactions were carried out with 4 equivalents of Bu_4NF; 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. ^1H 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 4*H*-Benzo[1,3]thiazines (4a–f). A solution of Bu_4NF 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_2Cl_2 (15 mL) at 0 °C and stirred at this temperature for 1 h. The reaction mixture was then quenched with H_2O and the resulting mixture was extracted with 3 X 20 mL portions of CH_2Cl_2. The combined extracts were dried (Na_2SO_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-4*H*-benzo[*e*][1,3]thiazine (4a) was obtained as a colorless solid, mp 142 °C ($CHCl_3$/hexanes) in 94% yield (132 mg). ^{1}H NMR (400 MHz, $CDCl_3$) 1.76 (4H, m, 2xCH_2), 3.54 (4H, m, CH_2NCH_2), 3.84 (3H, s, 5-OCH_3), 4.51 (2H, s, 4-CH_2), 6.41 (1 H, d, *J* =8 Hz, 6-H), 6.92 (1H, d *J* =7 Hz, 7-H), 7.17–7.20 (1H, m, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$) 25.3 (2 x CH_2), 49.5 (CH_2NCH_2), 53.8 (CH_2 C_4), 56.1 (5-OCH_3), 125.1 (C_{4a}), 126.3 (C_5), 128.7 (C_6), 131.3 (C_7), 134.2 (C_8), 155.6 (C_{8a}), 156.8 (C_2). Anal. Calcd for $C_{13}H_{16}N_2OS$: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.84; H, 6.42; N, 11.23.

2-(Pyrrolidin-1-yl)-4*H*-benzo[*e*][1,3]thiazine (4b) was obtained as a colorless solid, mp 120 °C ($CHCl_3$/hexanes), in 91% yield (124 mg). ^{1}H NMR (400 MHz, $CDCl_3$) 1.93 (4H, m, 2 x CH_2), 3.52–3.56 (4H, m, CH_2NCH_2), 4.55 (2H, s, 4-CH_2), 7.41 (2H, m, 5-H, 8-H), 7.86–7.89 (2H, m, 6-H, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$) 25.7 (2 x CH_2), 46.3 (-NCH_2), 48.8 (-NCH_2), 52.4 (CH_2 C_4), 109.5 (C_{4a}), 119.7 (C_5), 123.6 (C_6), 127.8 (C_7), 133.2 (C_8), 154.8 (C_{8a}), 156.4 (C_2). Anal. Calcd for $C_{12}H_{14}N_2S$: C, 66.02; H, 6.46; N, 12.83. Found: C, 66.15; H, 6.51; N, 12.87.

2-Diisopropylamino-4*H*-benzo[*e*][1,3]thiazine (**4c**) was obtained as a light brown solid, mp 134 °C ($CHCl_3$/hexanes), in 83% yield (145 mg). ^{1}H NMR (400 MHz, $CDCl_3$) 1.33 (12H, t, *J* = 5 Hz, 4 x CH_3), 4.05 (2 H, m, 2 x NCH), 4.21 (2H, s, 4-CH_2), 7.45–7.48 (2H, m, 5-H, 8-H), 7.85 (2 H, m, 6-H, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$) 21.5 (2 x CH_3), 22.7 (2 x CH_3), 48.4 (NCH), 51.2 (NCH), 53.5 (CH_2 C_4), 121.5 (C_{4a}), 122.3 (C_5), 124.7 (C_6), 125.3 (C_7), 133.21 (C_8), 154.1 (C_{8a}), 159.3 (C_2). Anal. Calcd for $C_{14}H_{20}N_2S$: C, 67.70; H, 8.12; N, 11.28. Found: C, 67.66; H, 8.05; N, 11.19.

2-(Morpholin-4-yl)-4*H*-benzo[*e*][1,3]thiazine (**4d**) was obtained as a colorless solid, mp 128 °C ($CHCl_3$/hexanes), in 89% yield (250 mg). ^{1}H NMR (400 MHz, $CDCl_3$) 3.56–3.60 (4H, m, CH_2OCH_2), 3.71 (4H, m, CH_2NCH_2), 4.15 (2H, s, 4-CH_2), 7.50 (2H, m, 5-H, 8-H), 7.85 (2H, m, 6-H, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$) 47.2 (CH_2OCH_2), 52.7 (CH_2NCH_2), 66.8 (CH_2 C_4), 122.5 (C_{4a}), 125.0 (C_5), 125.6 (C_6), 127.9 (C_7), 128.4 (C_8), 151.7 (C_{8a}), 163.3 (C_2). Anal. Calcd for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.96. Found: C, 61.57; H, 6.09; N, 11.91.

2-Diethylamino-4*H*-benzo[*e*][1,3]thiazine (**4e**) was obtained as a colorless liquid in 94% yield (135 mg). ^{1}H NMR (400 MHz, $CDCl_3$) 1.28 (6 H, t, *J* = 6 Hz, 2 x CH_3), 3.57 (4H, q, *J* = 6.0 Hz, CH_2NCH_2), 4.31 (2H, s, 4-CH_2), 7.25 (2H, m, 5-H, 8-H), 7.45–7.49 (2H, m, 6-H, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$) 13.91 (2 x CH_3), 43.3 (CH_2NCH_2), 56.6 (CH_2 C_4), 125.4 (C_{4a}), 125.4 (C_5), 126.9 (C_6), 127.7 (C_7), 132.1 (C_8), 135.4 (C_{8a}), 158.2 (C_2). Anal. Calcd for $C_{12}H_{16}N_2S$: C, 65.41; H, 7.32; N, 12.71. Found: C, 65.38; H, 7.36; N, 12.69.

2-Dimethylamino-4*H*-benzo[*e*][1,3]thiazine (**4f**) was obtained as a brown solid, mp 74–76 °C ($CHCl_3$/hexanes), in 80% yield (118 mg). ^{1}H NMR (400 MHz, $CDCl_3$) 3.18 (6H, s, CH_3NCH_3), 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, $CDCl_3$) 41.2 (CH_3NCH_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 $C_{10}H_{12}N_2S$: C, 62.46; H, 6.29; N, 14.57. Found: C, 62.47; H, 6.32; N, 14.59.

2-Dimethylamino-5, 8-dimethoxy-4*H*-benzo[*e*][1,3]thiazine (**4g**) was obtained as a light red liquid in 95% yield (126 mg). ^{1}H NMR (400 MHz, $CDCl_3$) 3.28 (6H, s, CH_3NCH_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, $CDCl_3$) 41.3 (CH_3NCH_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 $C_{12}H_{16}N_2O_2S$: 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-4*H*-benzo[*e*][1,3]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, $CDCl_3$) 1.94 (4 H, m, 2 x CH_2), 3.48–3.51 (4 H, m, CH_2NCH_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* = 8Hz, 6-H), 6.81 (1 H, d, J = 8Hz, 7-H). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06. Found: C, 60.45; H, 6.47; N, 10.11.

6, 7-Dimethoxy-2-dimethylamino-4*H*-benzo[*e*][1,3]thiazine (**4i**) was obtained as colorless solid, mp 135°C ($CHCl_3$/hexanes), in 89% yield (129 mg). ^{1}H NMR (400 MHz, $CDCl_3$) 1.58 (6H, s, CH_3NCH_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, $CDCl_3$) 40.6 (CH_3NCH_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 $C_{12}H_{16}N_2O_2S$: 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_2Cl_2 (15 mL) was added a THF solution of Bu_4NF (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_2Cl_2 and washing with water, the combined organic phases were dried (Na_2SO_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, $CDCl_3$). 1.86 (4 H, m, 2 x CH_2), 3.61

(4 H, m, CH_2NCH_2), 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). ^{13}C NMR (100 MHz, $CDCl_3$) 26.5, 49.2, 121.2, 124.5, 125.1, 126.3, 128.5, 130.4, 164.8.

3-Diisopropylamino-1,2-benzisothiazole (**7b**) was obtained as a light brown solid, mp 89 °C ($CHCl_3$/ hexanes), in 86 % yield (186 mg). ^{1}H NMR (400 MHz, $CDCl_3$) 1.34 (12H, t, *J* = 5.0 Hz, 4 x CH_3), 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). ^{13}C NMR (100 MHz, $CDCl_3$) 22.4, 50.1, 120.6, 124.0, 124.9, 127.4, 132.1, 152.3, 163.4. Anal. Calcd for $C_{13}H_{18}N_2S$: 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-benzisothiazole (7c) was obtained as colorless solid, mp 53 °C ($CHCl_3$/hexanes) (lit.,[21] mp 52-53 °C), in 94% yield (146 mg). ^{1}H NMR (400 MHz, $CDCl_3$) 3.56 (4H, t, *J* = 4.7 Hz, CH_2-NCH_2), 3.95 (4H, t, *J* = 4.6Hz, CH_2-O-CH_2), 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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). ^{1}H NMR (400 MHz, $CDCl_3$) 1.31 (6H, t, *J* = 7.0 Hz, 2 x CH_3), 3.64 (4H, q, *J* = 7.0 Hz, 2 x CH_2), 7.34 (1H, t, *J* = 7.8 Hz, H-5), 7.45 (1H, t, *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); ^{13}C NMR (100 MHz, $CDCl_3$) 13.8, 45.6, 120.8, 124.0, 124.6, 127.5, 128.3, 153.3, 162.5. Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58. Found: C, 64.10; H, 6.75; N, 13.41.

3-Dimethylamino-1,2-benzisothiazole (**7e**) was obtained as a colorless solid, mp 94 °C ($CHCl_3$/ hexanes), in 91% yield (185 mg). ^{1}H NMR (400 MHz, $CDCl_3$) 3.23 (6H, br s, CH_3NCH_3), 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); ^{13}C NMR (100 MHz, $CDCl_3$) 42.2, 120.8, 124.0, 124.8, 127.7, 128.2, 153.4, 164.4. Anal. Calcd for $C_9H_{10}N_2S$: 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). ^{1}H NMR (400 MHz, $CDCl_3$) 1.82 (6H, br s, 3 x CH_2), 3.49 (4H, br s, CH_2NCH_2), 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* = 6.5Hz, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{12}H_{14}N_2S$: 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 ($CHCl_3$/hexanes), in 82% yield (195 mg). ^{1}H NMR (400 MHz, $CDCl_3$) □ 1.92 (4H, m, 2 x CH_2), 3.59 (4H, m, CH_2NCH_2), 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); ^{13}C NMR (100 MHz, $CDCl_3$) □ 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 $C_{15}H_{14}N_2S$: 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 ($CHCl_3$/hexanes), in 92 % yield (150 mg). ^{1}H NMR (400 MHz, $CDCl_3$) □ 1.41 (12H, t, *J* = 5.1 Hz, 4 x CH_3), 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-8), 8.01 (1H, d, *J* = 8.0 Hz, H-5), 8.25 (1H, s, H-9), 8.49 (1H, s, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) □ 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 $C_{17}H_{20}N_2S$: 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 ($CHCl_3$/hexanes), in 94 % yield (148 mg). ^{1}H NMR (400 MHz, $CDCl_3$) □ 3.66 (4H, t, *J* = 4.8 Hz, CH_2N-CH_2), 4.02 (4H, t, *J* = 4.7 Hz, CH_2-O-CH_2), 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); ^{13}C NMR (100 MHz, $CDCl_3$) □ 51.0, 67.2, 118.6, 123.7, 125.9, 127.7, 127.9, 127.9, 129.5, 130.6, 133.0, 148.1, 163.8. Anal. Calcd for $C_{15}H_{14}N_2OS$: 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). ^{1}H NMR (400 MHz, $CDCl_3$) □ 1.38 (6H, t, *J* = 7.0 Hz, 2 x CH_3), 3.74 (4H, q, *J* = 7.0 Hz, CH_2N-CH_2), 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); ^{13}C NMR (100 MHz, $CDCl_3$) □ 13.8, 45.7, 118.1, 124.2, 125.5, 127.5, 127.7, 128.4, 129.8, 130.5, 132.7, 148.4, 162.1. Anal. Calcd for $C_{15}H_{16}N_2S$: 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 ($CHCl_3$/hexanes), in 81% yield (185 mg). ^{1}H NMR (400 MHz, $CDCl_3$) □ 3.34 (6H, s, CH_3NCH_3), 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); ^{13}C NMR (100 MHz, $CDCl_3$) □ 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 $C_{13}H_{12}N_2S$: 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 ($CHCl_3$/ hexanes), in yield of 96% (174 mg). ^{1}H NMR (400 MHz, $CDCl_3$) 1.58 (6H, br s, 3 x CH_2), 3.60 (4H, br s, CH_2NCH_2), 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{16}H_{16}N_2S$: C, 71.61; H, 6.01; N, 10.44. Found: C, 71.54; H, 5.87; N, 10.36.

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