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NOVEL METHOD FOR THE SYNTHESIS OF 3-MONOSUBSTITUTED SIX-MEMBERED BENZOSULTAMS

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Abstract – 3-Monosubstituted six-membered benzosultams with a wide range of functional groups were prepared by simple and convenient two-step procedures. *o*-Lithiation of *N*-Boc-*o*-toluenesulfonamide followed by reaction with aldehydes gave carbinol sulfonamides, which were converted to 3-monosubstituted six-membered benzosultams via TMSCl/NaI/MeCN reagent mediated cyclization. The mechanism and the scope of this novel transformation are studied.

INTRODUCTION

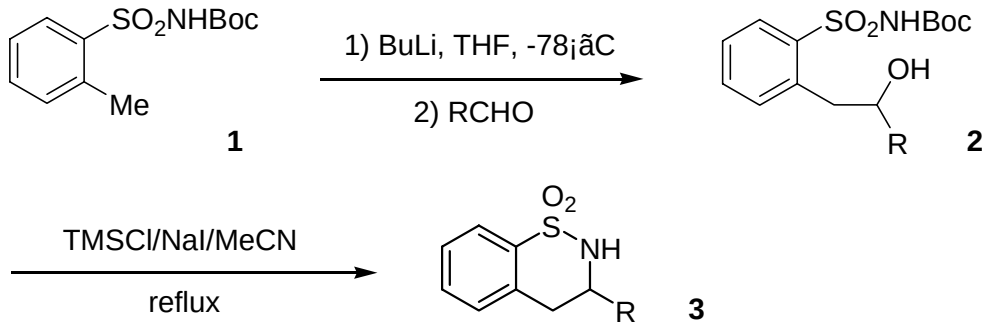
The importance of the sulfonamide unit in medicinal chemistry cannot be overstated.[1] Sulfonamides have been shown to exhibit a wide spectrum of biological activities and constitute an important class of drugs, with several types of pharmacological agents possessing antibacterial, anti-carbonic anhydrase, diuretic, hypoglycemic, antithyroid, antiviral and anticancer activity among others.[2] In addition to being a carboxyl isostere, the introduction of the SO_2-N moiety induces an increase of stability, for example, towards protease-catalyzed degradation in the case of sulfonamide-containing peptidomimetics.[3] Recently, conformationally constrained sulfonamides (sultams) have served as key functional groups in the development of: nonsteroidal antiinflammatory agents, agonists of 5-HT_{1A} receptors, novel serine inhibitors, zinc enzyme carbonic anhydrase inhibitors, etc.[4] Beyond their significance in the treatment of diseases, sultams have also been employed with considerable success as chiral auxiliaries in asymmetric versions of several reactions, including alkylations, acylations, aldol reactions, Diels-Alder reactions and azidations.[5] Synthesis of *N*-fluorobenzosultam templates has become one of the important strategies for the development of novel electrophilic fluorinating agents.[6]

As part of a program to study the biological activities of highly functionalized cyclic sulfonamides, we are interested in the development of an efficient method for the construction of 3-monosubstituted six-membered benzosultams, especially for the synthesis of 3-arylated analogues. Takeuchi's group reported a simple way to prepare such benzosultams from *N*-acyl-*o*-toluenesulfonamide in two steps via ortho-methyl lithiation/cyclization processes followed by Pd/C catalyzed hydrogenation.[7] The yields for

the cyclization were highly dependent on the bulkiness of the acyl substituents (RCO-, R = *t*-Bu, 74%; *c*-Hex, 54%; *i*-Pr, 46%; *i*-Bu, 20%; Ph, 25%; Me, 0%), the bulky *t*-butyl worked best with a moderate yield, whereas the small methyl group failed to be introduced into the 3-position. The low yields and substrate limitations make this method not very useful. There are other ways to prepare *N*-methyl or phenyl substituted six-membered benzosultams,[8] however, the difficulty in removing the methyl or phenyl protective group at the nitrogen atom limited their applications. Thus, a simple and general procedure to generate 3-monosubstituted six-membered benzosultams, which can tolerate a wide variety of functional groups, remains elusive. In our previous researches, we demonstrated that both 3,3-disubstituted five- and six-membered benzosultams can be constructed very efficiently via the TMSCl/NaI/MeCN reagent mediated novel cyclization.[9] To study the mechanism, scope and limitations of this novel methodology, we hereby report the application of TMSCl/NaI/MeCN reagent in the synthesis of 3-monosubstituted six-membered benzosultams.

RESULTS AND DISCUSSION

The first step takes advantage of the powerful sulfonamide directed *ortho* metalation (D*o*M)[10] effect. *N*-Boc-*o*-toluenesulfonamide **1** underwent *ortho*-methyl metalation, as well as *N*-metalation, with two equivalents of BuLi in anhydrous THF under nitrogen atmosphere at –78°C for 30 min to form dilithiosulfonamide, which was reacted with an aldehyde to form a carbinol (Scheme 1).



Scheme 1

Keen to test the generality of our strategy, a wide range of aldehydes, including aliphatic and functionally substituted aromatic aldehydes, were used, and the corresponding carbinol sulfonamides **2a-l** were obtained in high yields, the results are outlined in Table 1.

With the carbinol sulfonamides readily available, we next tested the cyclization promoted by TMSCl/NaI/MeCN reagent. As is expected, when substrate **2a** was subjected to two equivalents of TMSCl and NaI in acetonitrile under reflux conditions for 1.5 h, the cyclization went smoothly to produce the benzosultam **3a** in 84% yield. Sultams **3b-l** were obtained in the same way (Table 1). As can be seen

from Table 1, this procedure is especially effective for the preparation of 3-monoarylated benzosultams, a number of important functional groups that include both electron donating, withdrawing ones, such as chloro-, fluoro-, dimethylamino-, methoxy-, cyano-, are tolerant to the reaction conditions. For the less bulky aliphatic substituents at the 3-position, the yields are moderate (entries i and j), but for the bulky aliphatic substituents like cyclohexyl and *tert*-butyl (entries k and l), the yields are less than satisfactory even for an extended reaction time (10 h). It is also of note that 3-methylated bezosultam (**3i**) which was unavailable by Takeuchi's method are readily obtained by TMSCl/NaI/MeCN reagent mediated novel transformation.

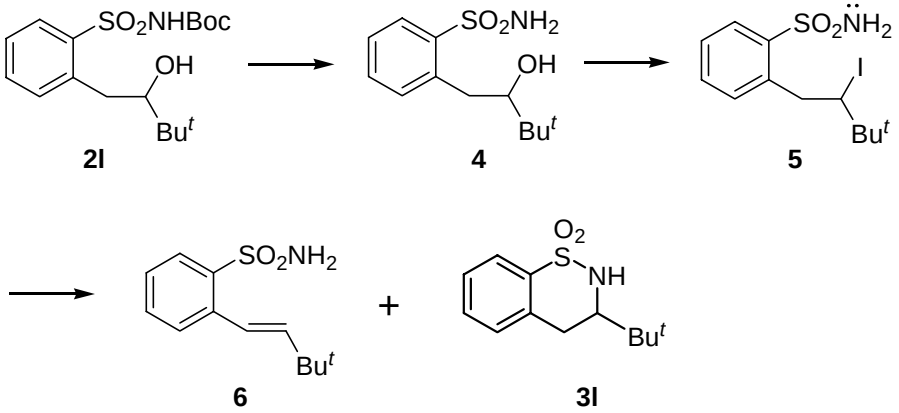
Table 1. Synthesis of 3-monosubstituted benzosultams

Entry	R	Yields (%)	Yield (%)
		2a-l	**3a-l**
a	phenyl	92	84
b	4-chlorophenyl	87	81
c	4-fluorophenyl	79	86
d	4-dimethylaminophenyl	88	82
e	4-methoxyphenyl	86	82
f	3,4-dimethoxyphenyl	82	90
g	3,4,5-trimethoxyphenyl	77	86
h	4-cyanophenyl	81	78
i	methyl	78	75
j	ethyl	80	72
k	cyclohexyl	86	46[a]
l	*t*-butyl	78	25[a]

[a] refluxed for 10 h

The TMSCl/NaI/MeCN system is well-known as a versatile reagent for reaction with many functional groups.[11] We assumed that the novel cyclization mediated by the TMSCl/NaI/MeCN reagent may proceed through a sequence of consecutive processes, involving in removing the Boc- protective group in the carbinol sulfonamide **2**, conversion of the hydroxy group to iodide, and an intramolecular nucleophilic substitution for the cyclization. In fact, when substrate **2l** was treated with two equivalents of TMSCl and NaI in acetonitrile at room temperature for 2 hours, the *N*-Boc protective group was cleared thoroughly to form the carbinol sulfonamide **4**, which was turned into the iodide **5** rather slowly at room temperature and only 25% iodide **5** was formed after 16 hours. When heated, substrate **2l** was converted to the iodide

5 much quickly (about 30 min). After heating for 10 hours, we isolated the cyclization product **3l** (25%), the elimination product **6** (42%), along with the unreacted iodide **5** (20%) (Scheme 2). It is apparent that the intramolecular nucleophilc substitution (cyclization) and elimination reactions are competitive, and the sterically hindered iodide **5** with a benzylic hydrogen favors the elimination, so the olefin **6** thus formed is predominant. Since a benzenesulfonamide is a weak nucleophile, the cyclization step may highly depend on the nature of the iodide. The bulky alkyl iodides (entries k and l) are less reactive than the less bulky ones (entries i and j) and the benzyl iodides in the bimolecular nucleophilic substitution, so the corresponding 3-monoalkylated benzosultams with a bulky substituents like cyclohexyl and *tert*-butyl are obtained in much lower yields.



Scheme 2

Numerous natural products, such as flavanoids, phenolic acids, tannins, stilbenes and lignans, have the key polyphenolic or polymethoxyphenolic units. These polyphenolic substances have a wide range of biological activities and are on the hot topics as nutritious antioxidants, in the prevention and treatment of cardiovascular diseases, cancers, osteoporosis, diabetes and neurodegenerative diseases.[12] By our novel method, the methoxyphenolic and polymethoxyphenolic benzosultams are available for the first time.

In conclusion, we have developed a new synthetic approach for the facile preparation of the 3-monosubstituted six-membered benzosultams via the novel cyclization mediated by TMSCl/NaI/MeCN reagent. The mechanism, scope and limitations of this novel transformation is also elucidated. Our method is superior and complementary to Tacheuchi's method in the synthesis of 3-monosubstituted six-membered benzosultams. Application of this reaction towards the synthesis of benzosultam libraries is now underway.

EXPERIMENTAL

Melting points were determined on an X-6 micro-melting point apparatus (Beijing Tech. Co., Ltd) and are

uncorrected. IR spectra (cm^{-1}) were recorded on a Perkin-Elmer 1600 spectrometer. ^1H NMR (600 MHz) spectra were recorded at room temperature for $CDCl_3$ solutions. All chemical shifts were reported as δ values (ppm) relative to Me_4Si (0.00 ppm) as internal standards for ^1H spectra. Electrospray-ionization mass spectrometry (ESI-MS) was performed on an API 4000 instrument. HRMS was measured on a Finnigan LC Q^{DECA} mass spectrometer. Microanalyses were performed with a YANAKO CHN-coder MT-5. Column chromatography was performed on silica gel (200-300 mesh). All reactions involving oxygen- or moisture-sensitive compounds were carried out under a dry N_2 atmosphere. Unless otherwise noted, reagents were added by syringe. THF was distilled from sodium/benzophenone immediately prior to use.

***N*-Boc-2-(2-hydroxy-2-phenylethyl)benzenesulfonamide (2a).** 2.20 M solution of BuLi (3.70 mL, 8 mmol) in hexane was added cautiously dropwise over 5 min to a stirred solution of *N*-Boc-*o*-toluenesulfonamide (1.09 g, 4 mmol) in THF (18 mL) under nitrogen at -78°C. After 15 min, another solution of benzaldehyde (0.43 g, 4 mmol) in THF (5 mL) was added. The mixture was stirred for 1 h and quenched by careful addition of saturated aqueous NH_4Cl. The mixture was then extracted with EtOAc (4 × 15 mL) and the combined extracts were dried and evaporated under reduced pressure to leave a yellow oil, which was purified by column chromatography on silica using hexane-EtOAc (8:1) as eluent to give compound **2a** (1.3 g, 92%) as colorless oil: IR (neat) cm^{-1} 3480, 3220, 1740, 1341, 1148, 757; ^1H NMR δ 1.34 (s, 9H), 3.15 (s, 1H), 3.36 (dd, J = 14.0, 4.4 Hz, 1H), 3.51 (dd, J = 14.0, 8.8 Hz, 1H), 5.04 (dd, J = 8.8, 4.4 Hz, 1H), 7.28—7.33 (m, 2H), 7.36—7.39 (m, 2H), 7.41—7.44 (m, 3H), 7.54 (td, J = 7.5, 1.4 Hz, 1H), 7.94 (s, 1H), 8.19 (dd, J = 7.5, 1.4 Hz, 1H); MS *m/z* 376 $[M–H]^–$; HRMS calcd for $C_{19}H_{22}NO_5S$: 376.1218; found: 376.1214.

***N*-Boc-2-[2-(4-chlorophenyl)-2-hydroxyethyl]benzenesulfonamide (2b).** From *N*-Boc-*o*-toluene-sulfonamide (1.09 g, 4 mmol), BuLi (2.20 M, 3.70 mL, 8 mmol) and 4-chlorobenzaldehyde (0.56 g, 4 mmol), compound **2b** (1.42 g, 87%) was obtained as a white solid after purification by silica gel column chromatography (20% EtOAc in hexane). mp 124–126 °C; IR (KBr) cm^{-1} 3525, 3218, 1748, 1345, 1216, 758; ^1H NMRδ1.36 (s, 9H), 2.91 (s, 1H), 3.41 (dd, J = 14.0, 4.4 Hz, 1H), 3.53 (dd, J = 14.0, 8.6 Hz, 1H), 4.69 (dd, J = 8.6, 4.4 Hz, 1H), 7.10 (d, J = 7.7 Hz, 1H), 7.21 (d, J = 7.7 Hz, 2H), 7.30 (d, J = 7.7 Hz, 2H), 7.34 (m, 1H), 7.44 (m, 2H), 7.99 (d, J = 7.7 Hz, 1H); MS *m/z* 410 $[M–H]^–$; Anal. Calcd for $C_{19}H_{22}ClNO_5S$: C, 55.40; H, 5.38; N, 3.40. Found: C, 55.32; H, 5.47; N, 3.58.

***N*-Boc-2-[2-(4-fluorophenyl)-2-hydroxyethyl]benzenesulfonamide (2c).** From *N*-Boc-*o*-toluene-sulfonamide (1.09 g, 4 mmol), BuLi (2.20 M, 3.70 mL, 8 mmol) and 4-fluorobenzaldehyde (0.50 g, 4 mmol), compound **2c** (1.25 g, 79%) was obtained as a white solid after purification by silica gel column chromatography (15% EtOAc in hexane). mp 114–116 °C; IR (KBr) cm^{-1} 3528, 3225, 1740, 1350, 1216, 758; ^1H NMR δ 1.38 (s, 9H), 2.48 (s, 1H), 3.44 (dd, J = 14.6, 4.4 Hz, 1H), 3.57 (dd, J = 14.6, 8.6 Hz, 1H),

4.65 (dd, *J* = 8.6, 4.4 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.51—7.62 (m, 4H), 7.89 (s, 1H), 8.11 (d, *J* = 7.7 Hz, 1H); MS *m/z* 394 $[M–H]^-$; Anal. Calcd for $C_{19}H_{22}FNO_5S$: C, 57.71; H, 5.61; N, 3.54. Found: C, 57.66; H, 5.42; N, 3.79.

***N*-Boc-2-[2-(4-dimethylaminophenyl)-2-hydroxyethyl]benzenesulfonamide (2d).** From *N*-Boc-*o*-toluenesulfonamide (1.09 g, 4 mmol), BuLi (2.20 M, 3.70 mL, 8 mmol) and 4-dimethylaminobenzaldehyde (0.60 g, 4 mmol), compound **2d** (1.46 g, 88%) was obtained as a yellow solid after purification by silica gel column chromatography (20% EtOAc in hexane). mp 123–125 °C; IR (KBr) cm^{-1} 3210, 1738, 1340, 1150, 758; ^1H NMR δ 1.32 (s, 9H), 2.66—2.69 (m, 6H), 2.98 (s, 1H), 3.45 (dd, *J* = 14.4, 4.4 Hz, 1H), 3.57 (dd, *J* = 14.4, 8.9 Hz, 1H), 4.77 (dd, *J* = 8.9, 4.4 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 2H), 7.04—7.24 (m, 3H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 8.07(s, 1H); MS *m/z* 419 $[M–H]^-$; Anal. Calcd for $C_{21}H_{28}N_2O_5S$: C, 59.98; H, 6.71; N, 6.66. Found: C, 59.82; H, 6.56; N, 6.74.

***N*-Boc-2-[2-hydroxy-2-(4-methoxyphenyl)ethyl]benzenesulfonamide (2e).** From *N*-Boc-*o*-toluenesulfonamide (1.09 g, 4 mmol), BuLi (2.20 M, 3.70 mL, 8 mmol) and 4-methoxybenzaldehyde (0.54 g, 4 mmol), compound **2e** (1.41 g, 86%) was obtained as a white solid after purification by silica gel column chromatography (25% EtOAc in hexane). mp 119–121 °C; IR (KBr) cm^{-1} 3480, 3221, 1742, 1340, 1150, 756; ^1H NMR δ 1.36 (s, 9H), 2.68 (s, 1H), 3.11 (dd, *J* = 14.0, 4.6 Hz, 1H), 3.29 (dd, *J* = 14.0, 8.8 Hz, 1H), 3.78 (s, 3H), 4.88 (dd, *J* = 8.8, 4.6 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 2H), 7.27 (td, *J* = 7.6, 1.1 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 2H), 7.46 (m, 1H), 7.56 (td, *J* = 7.6, 1.1 Hz, 1H), 7.92 (s, 1H), 8.09 (dd, *J* = 7.6, 1.1 Hz, 1H); MS *m/z* 406 $[M–H]^-$; Anal. Calcd for $C_{20}H_{25}NO_6S$: C, 58.95; H, 6.18; N, 3.44. Found: C, 58.99; H, 6.21; N, 3.41.

***N*-Boc-2-[2-(3,4-dimethoxyphenyl)-2-hydroxyethyl]benzenesulfonamide (2f).** From *N*-Boc-*o*-toluenesulfonamide (1.09 g, 4 mmol), BuLi (2.20 M, 3.70 mL, 8 mmol) and 3,4-dimethoxybenzaldehyde (0.67 g, 4 mmol), compound **2f** (1.43 g, 82%) was obtained as a white solid after purification by silica gel column chromatography (25% EtOAc in hexane). mp 141–143 °C; IR (KBr) cm^{-1} 3520, 3220, 1744, 1328, 1148, 758; ^1H NMR δ 1.35 (s, 9H), 2.48 (s, 1H), 3.27 (dd, *J* = 14.6, 4.4 Hz, 1H), 3.44 (dd, *J* = 14.6, 8.6 Hz, 1H), 3.71—3.75 (m, 6H), 4.82 (dd, *J* = 8.6, 4.4 Hz, 1H), 6.86—6.95 (m, 3H), 7.05 (m, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.62 (s, 1H), 8.07 (dd, *J* = 7.7, 1.2 Hz, 1H); MS *m/z* 436 $[M–H]^-$; Anal. Calcd for $C_{21}H_{27}NO_7S$: C, 57.65; H, 6.22; N, 3.20. Found: C, 57.69; H, 6.40; N, 3.24.

***N*-Boc-2-[2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethyl]benzenesulfonamide (2g).** From *N*-Boc-*o*-toluenesulfonamide (1.09 g, 4 mmol), BuLi (2.20 M, 3.70 mL, 8 mmol) and 3,4,5-trimethoxybenzaldehyde (0.79 g, 4 mmol), compound **2g** (1.44 g, 77%) was obtained as a white solid after purification by silica gel column chromatography (25% EtOAc in hexane). mp 131–133 °C; IR (KBr) cm^{-1} 3518, 3224, 1740, 1310, 1145, 757; ^1H NMR δ 1.36 (s, 9H), 2.36 (s, 1H), 3.37 (dd, *J* = 14.0,

8.6 Hz, 1H), 3.64 (dd, *J* = 14.0, 4.4 Hz, 1H), 3.68—3.71 (m, 9H), 4.82 (dd, *J* = 8.6, 4.4 Hz, 1H), 6.81 (d, *J* = 1.2 Hz, 2H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.44 (td, *J* = 7.6, 1.2 Hz, 1H), 7.50 (td, *J* = 7.6, 1.2 Hz, 1H), 7.82 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.32 (s, 1H); MS *m/z* 466 $[M–H]^-$; Anal. Calcd for $C_{22}H_{29}NO_8S$: C, 56.52; H, 6.25; N, 3.00. Found: C, 56.48; H, 6.19; N, 3.05.

***N*-Boc-2-[2-(4-cyanophenyl)-2-hydroxyethyl]benzenesulfonamide (2h).** From *N*-Boc-*o*-toluenesulfonamide (1.09 g, 4 mmol), BuLi (2.50 M, 3.20 mL, 8 mmol) and 4-cyanobenzaldehyde (0.53 g, 4 mmol), compound **2h** (1.30 g, 81%) was obtained as a yellow solid after purification by silica gel column chromatography (20% EtOAc in hexane). mp 125–126 °C; IR (KBr) cm^{-1} 3210, 2238, 1595, 1482, 757; ^1H NMR δ 1.35 (s, 9H), 2.42 (s, 1H), 3.26 (dd, *J* = 14.2, 8.4 Hz, 1H), 3.58 (dd, *J* = 14.2, 4.4 Hz, 1H), 4.77 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.38—7.41 (m, 3H), 7.54 (d, *J* = 7.6 Hz, 2H), 7.81 (d, *J* = 7.6 Hz, 1H), 8.22 (s, 1H); MS *m/z* 401 $[M–H]^-$; Anal. Calcd for $C_{20}H_{22}N_2O_5S$: C, 59.69; H, 5.51; N, 6.96. Found: C, 59.58; H, 5.60; N, 6.84.

***N*-Boc-2-(2-hydroxypropyl)benzenesulfonamide (2i).** From *N*-Boc-*o*-toluenesulfonamide (1.09 g, 4 mmol), BuLi (2.50 M, 3.20 mL, 8 mmol) and acetaldehyde (0.18 g, 4 mmol), compound **2i** (0.96 g, 78%) was obtained as a colorless oil after purification by silica gel column chromatography (30% EtOAc in hexane). IR (neat) cm^{-1} 3411, 1615, 1160, 750; ^1H NMR δ 1.30 (d, *J* = 6.2 Hz, 3H), 1.36 (s, 9H), 3.09 (dd, *J* = 14.4, 2.8 Hz, 1H), 3.31 (dd, *J* = 14.4, 10.2 Hz, 1H), 3.47 (m, 1H), 7.31 (m, 2H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.92 (s, 1H), 8.13 (d, *J* = 7.8 Hz, 1H); MS *m/z* 314 $[M–H]^-$; HRMS calcd for $C_{14}H_{20}NO_5S$: 314.1061; found: 314.1070.

***N*-Boc-2-(2-hydroxybutyl)benzenesulfonamide (2j).** From *N*-Boc-*o*-toluenesulfonamide (1.09 g, 4 mmol), BuLi (2.50 M, 3.20 mL, 8 mmol) and propionaldehyde (0.24 g, 4 mmol), compound **2j** (1.06 g, 80%) was obtained as a colorless oil after purification by silica gel column chromatography (30% EtOAc in hexane). IR (neat) cm^{-1} 3420, 1605, 1440, 1165, 757; ^1H NMR δ 0.95 (t, *J* = 5.8 Hz, 3H), 1.28 (m, 2H), 1.34 (s, 9H), 2.92 (s, 1H), 3.11 (dd, *J* = 14.0, 2.8 Hz, 1H), 3.26 (dd, *J* = 14.0, 10.2 Hz, 1H), 3.55 (m, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 8.05 (d, *J* = 7.6 Hz, 1H), 8.42 (s, 1H); MS *m/z* 328 $[M–H]^-$; HRMS calcd for $C_{15}H_{22}NO_5S$: 328.1218; found: 328.1227.

***N*-Boc-2-(2-cyclohexyl-2-hydroxyethyl)benzenesulfonamide (2k).** From *N*-Boc-*o*-toluenesulfonamide (1.09 g, 4 mmol), BuLi (2.20 M, 3.70 mL, 8 mmol) and cyclohexanecarboxaldehyde (0.45 g, 4 mmol), compound **2k** (1.32 g, 86%) was obtained as a colorless oil after purification by silica gel column chromatography (20% EtOAc in hexane). IR (neat) cm^{-1} 3420, 1738, 1338, 1160, 758; ^1H NMR δ 1.06—2.01 (m, 11H), 1.38 (s, 9H), 2.28 (s, 1H), 3.12 (dd, *J* = 14.1, 2.8 Hz, 1H), 3.34 (dd, *J* = 14.1, 10.7 Hz, 1H), 3.58 (m, 1H), 7.18 (d, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 8.12 (m, 2H); MS *m/z* 382 $[M–H]^-$; HRMS calcd for $C_{19}H_{28}NO_5S$: 382.1687; found: 382.1689.

***N*-Boc-2-(2-hydroxy-3,3-dimethylbutyl)benzenesulfonamide (2l).** From *N*-Boc-*o*-toluenesulfonamide

(1.09 g, 4 mmol), BuLi (2.20 M, 3.70 mL, 8 mmol) and 2,2-dimethylpropionaldehyde (0.35 g, 4 mmol), compound **2l** (1.10 g, 78%) was obtained as a colorless oil after purification by silica gel column chromatography (20% EtOAc in hexane). IR (neat) cm^{-1} 3410, 1740, 1335, 1161, 759; ^1H NMR δ 1.02 (s, 9H), 1.38 (s, 9H), 2.45 (s, 1H), 3.09 (dd, *J* = 14.1, 2.5 Hz, 1H), 3.28 (dd, *J* = 14.1, 10.8 Hz, 1H), 3.53 (dd, *J* = 10.8, 2.5 Hz, 1H), 7.39 (td, *J* = 7.6, 1.3 Hz, 1H), 7.44 (m, 1H), 7.58 (td, *J* = 7.6, 1.3 Hz, 1H), 7.89 (s, 1H), 8.13 (dd, *J* = 7.6, 1.3 Hz, 1H); MS *m/z* 356 $[M–H]^–$; HRMS calcd for $C_{17}H_{26}NO_5S$: 356.1531; found: 356.1528.

3-Phenyl-2*H*,4*H*-benzo[*e*][1,2]thiazine 1,1-dione (3a). Chlorotrimethylsilane (0.52 mL, 4 mmol) was added cautiously dropwise to a stirred solution of **2a** (0.76 g, 2 mmol) and sodium iodide (0.60 g, 4 mmol) in MeCN (10 mL) under nitrogen at rt. The mixture was heated under reflux for 1.5 h, after which it was cooled and 10% aqueous sodium thiosulfate was added. The mixture was extracted with EtOAc, and the combined organic layers was washed with 10% aqueous sodium thiosulfate, brine, dried (Na_2SO_4), concentrated in vacuo and chromatographed using hexane-EtOAc (7:1) as eluent to give compound **3a** (0.44 g, 84%) as a white solid: Mp and spectral data (^1H NMR, IR, MS) were in agreement with literature values.[7]

3-(4-Chlorophenyl)-2*H*,4*H*-benzo[*e*][1,2]thiazine 1,1-dione (3b). From **2b** (1.03 g, 2.5 mmol), chlorotrimethylsilane (0.65 mL, 5 mmol) and sodium iodide (0.75 g, 5 mmol), compound **3b** (0.61 g, 84%) was obtained as a white solid after purification by silica gel column chromatography (20% EtOAc in hexane). mp 169–171 °C; IR (KBr) cm^{-1} 3260, 1320, 1169, 754; ^1H NMR δ 3.21 (dd, *J* = 16.6, 11.5 Hz, 1H), 3.28 (dd, *J* = 16.6, 5.1 Hz, 1H), 4.72 (td, *J* = 11.5, 5.1 Hz, 1H), 4.96 (d, *J* = 11.5 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.21—7.25 (m, 4H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 1H); MS *m/z* 292 $[M–H]^–$; Anal. Calcd for $C_{14}H_{12}ClNO_2S$: C, 57.24; H, 4.12; N, 4.77. Found: C, 57.20; H, 4.22; N, 4.81.

3-(4-Fluorophenyl)-2*H*,4*H*-benzo[*e*][1,2]thiazine 1,1-dione (3c). From **2c** (0.80 g, 2 mmol), chlorotrimethylsilane (0.52 mL, 4 mmol) and sodium iodide (0.60 g, 4 mmol), compound **3c** (0.45 g, 81%) was obtained as a white solid after purification by silica gel column chromatography (20% EtOAc in hexane). mp 157–158 °C; IR (KBr) cm^{-1} 3257, 1334, 1160, 759; ^1H NMR δ 3.32 (dd, *J* = 16.6, 11.5 Hz, 1H), 3.45 (dd, *J* = 16.6, 5.1 Hz, 1H), 4.65 (td, *J* = 11.5, 5.1 Hz, 1H), 4.92 (d, *J* = 11.5 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.32—7.50 (m, 5H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H); MS *m/z* 276 $[M–H]^–$; Anal. Calcd for $C_{14}H_{12}FNO_2S$: C, 60.64; H, 4.36; N, 5.05. Found: C, 60.57; H, 4.31; N, 5.01.

3-(4-Dimethylaminophenyl)-2*H*,4*H*-benzo[*e*][1,2]thiazine 1,1-dione (3d). From **2d** (0.72 g, 1.7 mmol), chlorotrimethylsilane (0.45 mL, 3.4 mmol) and sodium iodide (0.51 g, 3.4 mmol), compound **3d** (0.42 g, 82%) was obtained as a white solid after purification by silica gel column chromatography (10% EtOAc in hexane). mp 172–174 °C; IR (KBr) cm^{-1} 3260, 1320, 1210, 757; ^1H NMR δ 2.86—2.88 (m, 6H), 3.47

(dd, *J* = 16.1, 11.4 Hz, 1H), 3.52 (dd, *J* = 16.1, 5.4 Hz, 1H), 4.02 (td, *J* = 11.4, 5.4 Hz, 1H), 4.61 (d, *J* = 11.4 Hz, 1H), 6.87—7.01(m, 5H), 7.47—7.52 (m, 2H), 7.62 (d, *J* = 7.6 Hz, 1H); MS *m/z* 301 $[M–H]^-$; Anal. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 6.00; N, 9.26. Found: C, 63.61; H, 6.26; N, 9.03.

3-(4-Methoxyphenyl)-2*H*,4*H*-benzo[*e*][1,2]thiazine 1,1-dione (3e). From **2e** (0.77 g, 1.9 mmol), chlorotrimethylsilane (0.50 mL, 3.8 mmol) and sodium iodide (0.57 g, 3.8 mmol), compound **3e** (0.45 g, 82%) was obtained as a white solid after purification by silica gel column chromatography (20% EtOAc in hexane). mp 147–149 °C; IR (KBr) cm^{-1} 3260, 1322, 1240, 757; ^1H NMR δ 3.20 (dd, *J* = 16.6, 11.5 Hz, 1H), 3.25 (dd, *J* = 16.6, 5.1 Hz, 1H), 3.72 (s, 3H), 4.42 (td, *J* = 11.5, 5.1 Hz, 1H), 4.82 (d, *J* = 11.5 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 2H), 7.08—7.16 (m, 3H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.52 (td, *J* = 7.7, 1.2 Hz, 1H), 7.71 (d, *J* = 7.7 Hz, 1H); MS *m/z* 288 $[M–H]^-$; Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.23; N, 4.84. Found: C, 62.14; H, 5.39; N, 4.78.

3-(3,4-Dimethoxyphenyl)-2*H*,4*H*-benzo[*e*][1,2]thiazine 1,1-dione (3f). From **2f** (0.96 g, 2.2 mmol), chlorotrimethylsilane (0.57 mL, 4.4 mmol) and sodium iodide (0.66 g, 4.4 mmol), compound **3f** (0.63 g, 90%) was obtained as a white solid after purification by silica gel column chromatography (20% EtOAc in hexane). mp 181–183 °C; IR (KBr) cm^{-1} 3240, 1323, 1220, 759; ^1H NMR δ 3.22 (dd, *J* = 16.6, 11.5 Hz, 1H), 3.29 (dd, *J* = 16.6, 5.2 Hz, 1H), 3.74—3.77 (m, 6H), 4.81 (td, *J* = 11.5, 5.2 Hz, 1H), 4.93 (d, *J* = 11.5 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 6.98 (d, *J* = 7.7 Hz, 1H), 7.08—7.38 (m, 3H), 7.46 (td, *J* = 7.7, 1.0 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 1H); MS *m/z* 318 $[M–H]^-$; Anal. Calcd for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.37; N, 4.39. Found: C, 60.22; H, 5.32; N, 4.41.

3-(3,4,5-Trimethoxyphenyl)-2*H*,4*H*-benzo[*e*][1,2]thiazine 1,1-dione (3g). From **2g** (0.93 g, 2 mmol), chlorotrimethylsilane (0.52 mL, 4 mmol) and sodium iodide (0.60 g, 4 mmol), compound **3g** (0.60 g, 86%) was obtained as a white solid after purification by silica gel column chromatography (15% EtOAc in hexane). mp 212–213 °C; IR (KBr) cm^{-1} 3249, 1316, 1220, 757; ^1H NMR δ 3.15 (dd, *J* = 16.6, 11.5 Hz, 1H), 3.26 (dd, *J* = 16.6, 5.4 Hz, 1H), 3.71—3.73 (m, 9H), 4.07 (td, *J* = 11.5, 5.4 Hz, 1H), 4.82 (d, *J* = 11.5 Hz, 1H), 6.25 (d, *J* = 1.2 Hz, 2H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.34 (td, *J* = 7.7, 1.2 Hz, 1H), 7.44 (td, *J* = 7.7, 1.2 Hz, 1H), 7.64 (d, *J* = 7.7 Hz, 1H); MS *m/z* 350 $[M+H]^+$, 367 $[M+NH_4]^+$; Anal. Calcd for $C_{17}H_{19}NO_5S$: C, 58.44; H, 5.48; N, 4.01. Found: C, 58.41; H, 5.32; N, 4.07.

3-(4-Cyanophenyl)-2*H*,4*H*-benzo[*e*][1,2]thiazine 1,1-dione (3h). From **2h** (0.61 g, 1.5 mmol), chlorotrimethylsilane (0.40 mL, 3 mmol) and sodium iodide (0.45 g, 3 mmol), compound **3h** (0.33 g, 78%) was obtained as a white solid after purification by silica gel column chromatography (15% EtOAc in hexane). mp 154–156 °C; IR (KBr) cm^{-1} 3310, 2230, 1590, 756; ^1H NMR δ 3.18 (dd, *J* = 16.1, 11.0 Hz, 1H), 3.22 (dd, *J* = 16.1, 5.4 Hz, 1H), 3.95 (td, *J* = 11.0, 5.4 Hz, 1H), 4.25 (d, *J* = 11.0 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.40—7.51 (m, 3H), 7.62—7.76 (m, 2H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H); MS *m/z* 283 $[M–H]^-$; Anal. Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.29; H, 4.33;

N, 9.76.

3-Methyl-2*H*,4*H*-benzo[*e*][1,2]thiazine 1,1-dione (3i). From **2i** (0.57 g, 1.8 mmol), chlorotrimethylsilane (0.47 mL, 3.6 mmol) and sodium iodide (0.54 g, 3.6 mmol), compound **3i** (0.27 g, 75%) was obtained as a white solid after purification by silica gel column chromatography (20% EtOAc in hexane). mp 129–130 °C; IR (KBr) cm^{-1} 3250, 1326, 1178, 758; ^{1}H NMR δ 1.33 (d, *J* = 6.0 Hz, 3H), 2.95 (dd, *J* = 17.1, 11.0 Hz, 1H), 3.02 (dd, *J* = 17.1, 5.4 Hz, 1H), 3.78 (m, 1H), 4.28 (d, *J* = 12.4 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.41 (td, *J* = 7.7, 1.2 Hz, 1H), 7.85 (dd, *J* = 7.7, 1.2 Hz, 1H); MS *m/z* 196 $[M–H]^–$; Anal. Calcd for $C_9H_{11}NO_2S$: C, 54.80; H, 5.62; N, 7.10. Found: C, 54.71; H, 5.73; N, 7.18.

3-Ethyl-2*H*,4*H*-benzo[*e*][1,2]thiazine 1,1-dione (3j). From **2j** (0.66 g, 2 mmol), chlorotrimethylsilane (0.52 mL, 4 mmol) and sodium iodide (0.60 g, 4 mmol), compound **3j** (0.31 g, 72%) was obtained as a white solid after purification by silica gel column chromatography (25% EtOAc in hexane). mp 134–136 °C; IR (KBr) cm^{-1} 3241, 1328, 1160, 758; ^{1}H NMR δ 0.95 (t, *J* = 6.1 Hz, 3H), 1.31 (m, 2H), 2.81 (dd, *J* = 16.4, 11.0 Hz, 1H), 2.96 (dd, *J* = 16.4, 5.4 Hz, 1H), 3.82 (m, 1H), 4.31 (d, *J* = 12.4 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.39 (td, *J* = 7.7, 1.2 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 1H); MS *m/z* 210 $[M–H]^–$; Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63. Found: C, 56.72; H, 6.27; N, 6.54.

3-Cyclohexyl-2*H*,4*H*-benzo[*e*][1,2]thiazine 1,1-dione (3k). From **2k** (0.81 g, 2.1 mmol), chlorotrimethylsilane (0.55 mL, 4.2 mmol) and sodium iodide (0.63 g, 4.2 mmol), compound **3k** (0.26 g, 46%) was obtained as a white solid after purification by silica gel column chromatography (10% EtOAc in hexane). Mp and Spectral data (^{1}H NMR, IR, MS) were in agreement with literature values.[7]

3-*t*-Butyl-2*H*,4*H*-benzo[*e*][1,2]thiazine 1,1-dione (3l). From **2l** (0.40 g, 1.1 mmol), chlorotrimethylsilane (0.30 mL, 2.2 mmol) and sodium iodide (0.33 g, 2.2 mmol), compound **3l** (0.066 g, 25%) was obtained as a white solid after purification by silica gel column chromatography (10% EtOAc in hexane). Mp and Spectral data (^{1}H NMR, IR, MS) were in agreement with literature values.[7]

Chlorotrimethylsilane (0.30 mL, 2.2 mmol) was added cautiously dropwise at rt to a stirred solution of **2l** (0.40 g, 1.1 mmol) and sodium iodide (0.33 g, 2.2 mmol) in MeCN (10 mL) under nitrogen. The reaction mixture was stirred at rt and the process was monitored by TLC. After 2 h, compound **2l** was disappeared. The solution was divided into two equal portions. One portion was added 10% aqueous sodium thiosulfate immediately. The mixture was extracted with EtOAc and the combined organic layers was washed with 10% aqueous sodium thiosulfate, brine, dried (Na_2SO_4), concentrated in vacuo and chromatographed using hexane-EtOAc (6:1) as eluent to give compound **4** (0.11g, 78%). The other portion was continued to react at rt for overnight. After the usual work up, the residue was chromatographed using hexane-EtOAc (10:1) as eluent to give production **4** (0.092g, 65%) and **5** (0.051,

25%).

2-(2-Hydroxy-3,3-dimethylbutyl)benzenesulfonamide (4). White solid; mp 102–104 °C; IR (KBr) 3310, 3218, 1502, 769 cm^{-1}; ^1H NMR δ 1.06 (s, 9H), 2.47 (s, 1H,), 3.11 (dd, *J* = 14.4, 8.1 Hz, 1H), 3.69 (dd, *J* = 14.4, 4.4 Hz, 1H), 3.88 (dd, *J* = 8.1, 4.4 Hz, 1H), 7.25—7.36 (m, 2H), 7.41 (s, 2H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H); MS *m/z* 256 $[M–H]^-$. Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.01; H, 7.44; N, 5.44. Found: C, 56.07; H, 7.49; N, 5.40.

2-(2-Iodo-3,3-dimethylbutyl)benzenesulfonamide (5). Colorless oil; IR (neat) 3455, 3022, 1735, 1540, 757 cm^{-1}. ^1H NMR δ 1.11 (s, 9H), 3.01 (dd, *J* = 14.4, 4.1 Hz, 1H), 3.64 (dd, *J* = 14.4, 8.6 Hz, 1H), 3.78 (dd, *J* = 8.6, 4.1 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.44 (td, *J* = 7.8, 1.2 Hz, 1H), 7.55 (s, 2H), 7.60 (t, *J* = 7.8 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H); MS *m/z* 366 $[M–H]^-$; HRMS calcd for $C_{12}H_{17}INO_2S$: 366.0024; found: 366.0027.

Chlorotrimethylsilane (0.30 mL, 2.2 mmol) was added cautiously dropwise to a stirred solution of **2l** (0.40 g, 1.1 mmol) and sodium iodide (0.33 g, 2.2 mmol) in MeCN (10 mL) under nitrogen at rt. The reaction mixture was refluxed for 10 h and was monitored by TLC. The solution was cooled and 10% aqueous sodium thiosulfate was added. The mixture was extracted with EtOAc, and the combined organic layer was washed with 10% aqueous sodium thiosulfate, brine, dried (Na_2SO_4), concentrated in vacuo and chromatographed using hexane-EtOAc (10:1) as eluent to give compound **5** (0.079g, 20%), **6** (0.11g, 42%), and **3l** (0.066g, 25%).

(*E*)-2-(3,3-dimethylbut-1-enyl)benzenesulfonamide (6). Yellow oil; IR (neat) 3320, 3055, 1740, 1638, 1528, 975 cm^{-1}; ^1H NMR δ 1.07 (s, 9H), 4.90 (s, 2H), 6.24 (d, *J* = 16.0 Hz, 1H), 7.12 (d, *J* = 16.0 Hz, 1H), 7.28—7.36 (m, 2H), 7.50 (td, *J* = 7.7, 1.2 Hz, 1H), 7.96 (t, *J* = 7.7 Hz, 1H); MS *m/z* 238 $[M–H]^-$; HRMS calcd for $C_{12}H_{16}NO_2S$: 238.0901; found: 238.0899.

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