# The Preparation of Benzoisothiazolo[1,2-*b*][1,2]isoquinolin-11-one-1,1-dioxides from Dilithiated *ortho*-Toluic Acids and Lithiated Methyl 2-(Aminosulfonyl)benzoate

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Select dilithiated *ortho*-toluic acids were prepared in excess lithium diisopropylamide and condensed with methyl 2-(aminosulfonyl)benzoate followed by a twofold cyclization of intermediates to afford benzoisothiazolo[1,2-*b*][1,2]isoquinolin-11-one-1,1-dioxides, a new fused-ring heterocyclic system.

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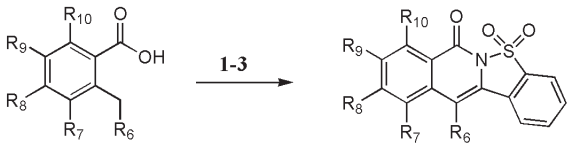
Several reports have dealt with the preparation and reactions of dilithiated *ortho*-toluic and related acids, where they have been condensed with a variety of electrophilic reagents including alkyl halides, carbonyl compounds and aromatic esters [1-5]. The *ortho*-phenacyl benzoic acids resulting from their ester condensation can be cyclized to isocoumarins or condensed-cyclized with hydrazines to afford dihydrobenzodiazepinones [2].

Methyl 2-(aminosulfonyl)benzoate has a considerable history for use in agriculture, especially for making sulfonamides, sulfonyl ureas and saccharin-related derivatives. Most of its reactions involve the sulfonamide functional group [6]. In a recent preliminary account involving this ester-sulfonamide, we reported the condensation-cyclization of this compound with polylithiated β-keto intermediates (*e.g.*, ketoesters, ketoamides), or its condensation-cyclization with organolithium or Grignard reagents to give 3-substituted 1,2-benzoisothiazole-1,1-dioxides [7].




**1** 5 LDA
**2** Methyl 2-(aminosulfonyl)-benzoate
**3** Aq. acid

**1-7**
**1** $R_6$-$R_{10}$ = H
**2** $R_6$ = $C_6H_5$, $R_7$-$R_{10}$ = H
**3** $R_9$ = $CH_3$, $R_6$-$R_8$ & $R_{10}$ = H
**4** $R_8$ = $CH_3$, $R_6$, $R_7$, $R_9$ & $R_{10}$ = H
**5** $R_8$ = $OCH_3$, $R_6$, $R_7$, $R_9$ & $R_{10}$ = H
**6** $R_{10}$ = $CH_3$, $R_6$-$R_9$ = H
**7** $R_7$ = $CH_3$, $R_6$, $R_8$-$R_{10}$ = H

]]Figure 1. Benzoisothiazolo[1,2-*b*][1,2]isoquinolin-11-one-1,1-dioxides, **1-7**.

During the current investigation several *ortho*-toluic acids were dilithiated with excess LDA (acid: LDA: ester-sulfonamide, 1:5:1) followed by condensation with methyl 2-(aminosulfonyl)benzoate. The intermediates were not isolated, and recrystallization of final products was completed with benzene-ethanol or xylenes-dimethylformamide (DMF). The products are substituted benzoisothiazolo-isoquinolinone-dioxides, benzoisothiazolo[1,2-*b*][1,2]isoquinolin-11-one-1,1-dioxides, **1-7** (Scheme 1) isolated in 50-96% yield. This is a new fused-ring system, and only a related fused-ring isomeric system has been reported [8]. The emphasis of this report was on the synthesis and pharmaceutical potential.

Structure elucidation for the fused-ring system came from X-ray crystallographic analysis of **6**. The molecular structure is shown in Figure 2, crystallographic data in Table 1, atomic positional parameters are listed in Table 2, and selected bond distances and angles are listed in Table 3. Data collected for crystals of $C_{16}H_{11}NO_3S$, **6,** and $C_{21}H_{13}NO_3S$, **2**, (not included) showed similar structures [9-11]. The structures of the products were also supported by absorption spectra (IR, $^1$H NMR, $^{13}$C NMR) and combustion analysis (for C, H, N). Routine absorptions, such as carbonyl IR absorptions for **1-7** 1660-1676 cm$^{-1}$, the $^1$H NMR methyl absorptions in **3-5**, and **7**, δ 2.73-2.95 ppm, were observed where expected, with the carbonyl carbon $^{13}$C-NMR for **4** displayed at δ 165.4 ppm [13]. Absorptions for the carbonyl carbon for other products were displayed, δ 164.1-167.7 ppm, (experimental section).

Initial results indicated [7] that the ideal ratios of reagents needed to be 1:5:1 (toluic acid: LDA: ester). When a 1:3:1 ratio was used [2], the yields of **1** and **2**

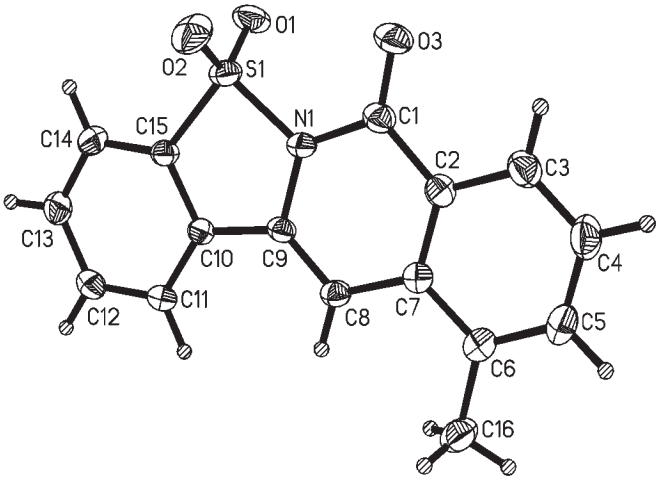



Figure 2. ORTEP diagram (50% ellipsoids for non-Hydrogen atoms) for $C_{16}H_{11}NO_3S$, **6**.

Table 1

Crystallographic Data for $C_{16}H_{11}NO_3S$, **6**

| | |
|---|---|
| Crystal Dimensions (mm) | 0.45 x 0.40 x 0.15 |
| Space Group | P -1 (#2) |
| *a* (Å) | 7.917(1) |
| *b* (Å) | 9.279(2) |
| *c* (Å) | 9.629(2) |
| α | 86.90(1)° |
| β | 85.69(1)° |
| γ | 69.62(1)° |
| *V* (Å$^3$) | 660.9(2) |
| fw | 297.33 |
| *Z* | 2 |
| $d_{calc}$ (g/cm$^3$) | 1.494 |
| μ (mm$^{-1}$) | 0.254 |
| trans. Factors | 0.902-1.015 |
| $R_1$ [a] | 0.0686 |
| $wR_2$ [b] | 0.1000 |
| Goodness of Fit | 4.020 |

[a] $R_1 = \Sigma(|F_o|-|F_c|)/\Sigma|F_o|$; [b] $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$.

Table 2

Atomic Positional Parameters for $C_{16}H_{11}NO_3S$, **6**

| atom | *x* | *y* | *z* | *U*(eq)* |
|---|---|---|---|---|
| S(1) | 1.32126(4) | 0.22125(3) | 0.91224(3) | 0.03875(8) |
| O(1) | 1.4206(1) | 0.27603(9) | 1.00101(9) | 0.0525(3) |
| O(2) | 1.4164(1) | 0.09424(8) | 0.8270(1) | 0.0584(3) |
| O(3) | 1.4361(1) | 0.4103(1) | 0.7010(1) | 0.0580(3) |
| N(1) | 1.1931(1) | 0.36935(9) | 0.81181(9) | 0.0341(2) |
| C(1) | 1.2725(2) | 0.4466(1) | 0.7143(1) | 0.0385(3) |
| C(2) | 1.1424(2) | 0.5704(1) | 0.6347(1) | 0.0355(3) |
| C(3) | 1.2123(2) | 0.6515(1) | 0.5331(1) | 0.0452(4) |
| C(4) | 1.0952(2) | 0.7693(1) | 0.4584(1) | 0.0550(4) |
| C(5) | 0.9099(2) | 0.8068(1) | 0.4832(1) | 0.0502(4) |
| C(6) | 0.8364(2) | 0.7284(1) | 0.5811(1) | 0.0403(3) |
| C(7) | 0.9550(1) | 0.6060(1) | 0.6596(1) | 0.0326(3) |
| C(8) | 0.8902(1) | 0.5184(1) | 0.7644(1) | 0.0333(3) |
| C(9) | 1.0069(1) | 0.4042(1) | 0.8374(1) | 0.0303(3) |
| C(10) | 0.9728(1) | 0.3028(1) | 0.9486(1) | 0.0306(3) |

Table 2 (continued)

| atom | *x* | *y* | *z* | *U*(eq)* |
|---|---|---|---|---|
| C(11) | 0.8076(1) | 0.3005(1) | 1.0060(1) | 0.0379(3) |
| C(12) | 0.8061(2) | 0.1961(1) | 1.1140(1) | 0.0417(3) |
| C(13) | 0.9657(2) | 0.0951(1) | 1.1645(1) | 0.0429(3) |
| C(14) | 1.1316(2) | 0.0940(1) | 1.1075(1) | 0.0397(3) |
| C(15) | 1.1305(1) | 0.1991(1) | 0.9999(1) | 0.0326(3) |
| C(16) | 0.6351(2) | 0.7722(1) | 0.6042(1) | 0.0547(4) |

*$U$(eq) defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

Table 3

Selected Bond Distances (Å) and Angles (°) for $C_{16}H_{11}NO_3S$, **6**

| | | | |
|---|---|---|---|
| S(1)-O(1) | 1.426(2) | C(5)-C(6) | 1.377(3) |
| S(1)-O(2) | 1.423(2) | C(6)-C(7) | 1.419(3) |
| S(1)-N(1) | 1.699(2) | C(6)-C(16) | 1.503(3) |
| S(1)-C(15) | 1.744(2) | C(7)-C(8) | 1.437(3) |
| O(3)-C(1) | 1.217(3) | C(8)-C(9) | 1.344(3) |
| N(1)-C(1) | 1.394(3) | C(9)-C(10) | 1.460(3) |
| N(1)-C(9) | 1.401(3) | C(10)-C(11) | 1.388(3) |
| C(1)-C(2) | 1.473(3) | C(10)-C(15) | 1.390(3) |
| C(2)-C(3) | 1.399(3) | C(11)-C(12) | 1.385(3) |
| C(2)-C(7) | 1.408(3) | C(12)-C(13) | 1.389(3) |
| C(3)-C(4) | 1.372(3) | C(13)-C(14) | 1.381(3) |
| C(4)-C(5) | 1.390(4) | C(14)-C(15) | 1.382(3) |

| | | | |
|---|---|---|---|
| O(1)-S(1)-O(2) | 118.7(1) | C(5)-C(6)-C(16) | 120.5(2) |
| O(1)-S(1)-N(1) | 109.64(9) | C(7)-C(6)-C(16) | 121.0(2) |
| O(1)-S(1)-C(15) | 111.9(1) | C(2)-C(7)-C(6) | 118.8(2) |
| O(2)-S(1)-N(1) | 109.4(1) | C(2)-C(7)-C(18) | 119.0(2) |
| O(2)-S(1)-C(15) | 111.9(1) | C(6)-C(7)-C(8) | 122.2(2) |
| N(1)-S(1)-C(15) | 91.90(9) | C(7)-C(8)-C(9) | 120.4(2) |
| S(1)-N(1)-C(1) | 121.1(2) | N(1)-C(9)-C(8) | 120.2(2) |
| S(1)-N(1)-C(9) | 114.1(1) | N(1)-C(9)-C(10) | 109.8(2) |
| C(1)-N(1)-C(9) | 124.8(2) | C(8)-C(9)-C(10) | 130.0(2) |
| O(3)-C(1)-N(1) | 120.4(2) | C(9)-C(10)-C(11) | 128.1(2) |
| O(3)-C(1)-C(2) | 125.5(2) | C(9)-C(10)-C(15) | 112.9(2) |
| N(1)-C(1)-C(2) | 114.1(2) | C(11)-C(10)-C(15) | 119.0(2) |
| C(1)-C(2)-C(3) | 117.4(2) | C(10)-C(11)-C(12) | 118.6(2) |
| C(1)-C(2)-C(7) | 121.4(2) | C(11)-C(12)-C(13) | 121.2(2) |
| C(3)-C(2)-C(7) | 121.2(2) | C(12)-C(13)-C(14) | 121.2(2) |
| C(2)-C(3)-C(4) | 119.0(2) | C(13)-C(14)-C(15) | 116.9(2) |
| C(3)-C(4)-C(5) | 120.3(2) | S(1)-C(15)-C(10) | 111.3(2) |
| C(4)-C(5)-C(6) | 122.2(2) | S(1)-C(15)-C(14) | 125.5(2) |
| C(5)-C(6)-C(7) | 118.4(2) | C(10)-C(15)-C(14) | 123.2(2) |

varied from 10-19 %, and the reproducibility of the procedure was inconsistent. Better yields were obtained with a 1:4:1 ratio, with the best yields occurring when the ratio was 1:5:1. Similar ratios of reagents were used when other polylithiated nucleophiles were condensed with anionic electrophiles [14].

The mechanistic sequence for the formation of these products can be envisioned to proceed by either, or both of two paths (path **one**: **A** + **B** → **D** → **E** → **G** → **H** → **1**; path **two**: **A** + **C** (**B** → **C**) → **F** → **F'** → **G** → **H** → **1**) with the initial formation of the *ortho*-phenacylbenzoic

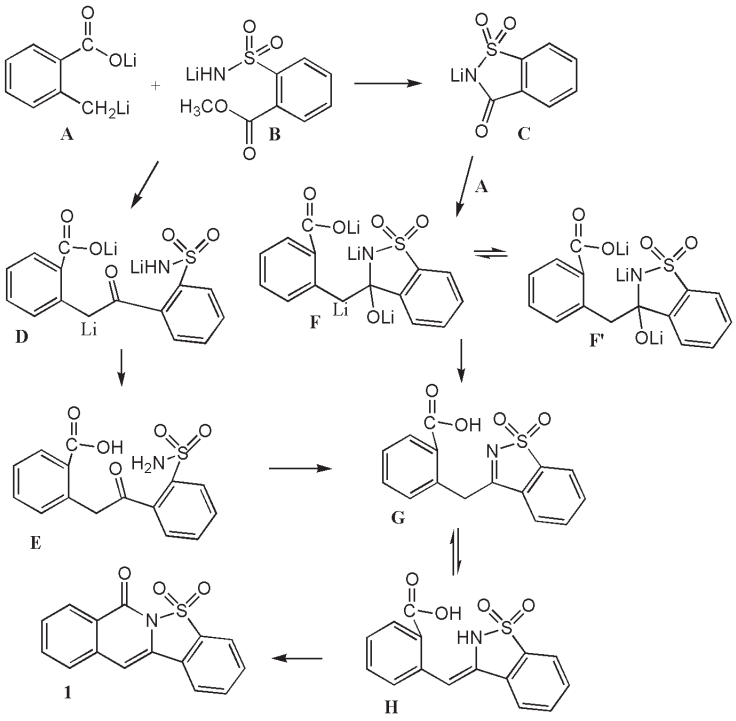


Figure 3. Mechanistic details for preparation of **1**.

acid/sulfonamide **D** resulting from **A** condensing with **B**, path **one**. Upon careful neutralization with acid (no reflux), intermediate **E** undergoes a twofold cyclization to **1**. Lithiated methyl 2-(aminosulfonyl)benzoate **B** also has the potential for cyclization to lithium saccharin **C**, upon treatment with lithium diisopropylamide (LDA) or a related base (**B** → **C**) [12], path **two**. The reaction medium in addition to a lengthy condensation time could accommodate tetralithiated intermediate **F** and more readily trilithiated intermediate **F'**. Upon acid neutralization to **G**, the second cyclization to **1** would occur.

In addition to a new ring system, the project demonstrates the developing potential for the condensation-cyclization of polylithiated systems using methyl 2-(aminosulfonyl)benzoate for the preparation of heterocyclic compounds. The new synthesis requires an experimental set-up that is on the order of complexity required for standard Grignard syntheses; the procedures can be reproduced by someone who is not necessarily experienced with strong base techniques. While the general procedure may not be under the optimal conditions for the preparation of a single compound, multi-gram quantities of pure products can be obtained, which is especially attractive for characterization, biological testing and other uses. The syntheses are regioselective, and the products were readily purified by recrystallization from routine solvents.

## EXPERIMENTAL

Melting points were obtained with a Mel-Temp II melting point apparatus in open capillary tubes and are uncorrected. Fourier Transform infrared spectra were obtained with a Nicolet Impact 410 FT-IR or a Mattson Genesis II FT-IR with Specac Golden Gate Accessory. Proton and $^{13}C$ nuclear magnetic resonance spectra were obtained with a Varian Associates Mercury Oxford 300 MHz (*ca*., 75 MHz for $^{13}C$ NMR), nuclear magnetic resonance spectrometer, and chemical shifts are recorded in δ ppm downfield from an internal tetramethylsilane (TMS) standard. Combustion analyses were performed by Quantitative Technologies, Inc., P.O. Box 470, Salem Industrial Park, Whitehouse, NJ 08888. Because the products have such high melting points, several recrystallizations were necessary to obtain analytical samples that required special combustion conditions that were requested at the time of sample submission.

Single crystal X-ray measurements for crystals of $C_{16}H_{11}NO_3S$, **6**, (light yellow, recrystallized from DMF) were collected on a Mercury CCD area detector coupled with a Rigaku AFC8 diffractometer with graphite monochromated Mo-Kα (λ = 0.71073 Å) radiation. The data were collected at a temperature of 22 °C to a maximum 2θ value of 27.79°. Data were collected in 0.30° oscillations in ω with 8 s exposures (two identical scans were performed at each position to identify detector anomalies). A sweep of data was done using ω oscillations from -90.0° to 90.0° at χ = 45.0° and ϕ = 0.0°; a second sweep was performed using ω oscillations from -30.0° to 30.0° at χ = 45.0° and ϕ = 90.0°.

The crystal-to-detector distance was 27.256 mm. The detector swing angle was 0.00°. Cell parameters and additional details of

the data collection are reported in Table 1.

Of the 5859 reflections collected, 2573 were unique ($R_{int}$ = 0.016); equivalent reflections were merged. Data were collected, processed, and corrected for Lorentz-polarization and for absorption using CrystalClear (Rigaku) [9]. The structures were solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined isotropically. The final cycle of full-matrix least-squares refinement on $F^2$ for $C_{16}H_{11}NO_3S$ **6** converged with $R_1$ = 0.0686 (all data).

Structure solution, refinement, and the calculation of derived results were performed using the *teXsan for Windows* [10] package of computer programs. Neutral atom scattering factors were those of Cromer and Waber [11], and the real and imaginary anomalous dispersion corrections were those of Cromer [15].

General Procedure for Preparation of Benzoisothiazolo[1,2-*b*][1,2]isoquinolin-11-one-1,1-dioxides **1-7** (Ratio of reagents – toluic acid: LDA: ester - 1:5:1) [7,14].

In a typical reaction sequence, LDA (0.079 mol) was prepared by the addition of 49-50 ml of 1.6 *M n*-butyllithium (0.079 mol) to a three-neck round-bottomed flask (*e.g.*, 500 ml), equipped with a nitrogen inlet tube, a side-arm addition funnel (*e.g.*, 125 ml), and a magnetic stir bar. The flask was cooled in an ice bath and 8.01 g (0.0788 mol) of diisopropylamine (Aldrich Chem. Co., 99.5%), dissolved in 35-50 ml of dry tetrahydrofuran (THF) (sodium/benzophenone – ketyl), was added from the addition funnel at a fast dropwise rate during a 5 min period (0°, $N_2$). The solution was stirred at 0° for an additional 15-20 min, and then treated *via* the addition funnel with 0.0150 mol of an *ortho*-toluic acid dissolved in 50-60 ml of THF. The addition time was 5 minutes. After 45-60 min at 0°, 3.47 g (0.0158 mol) of methyl 2-(aminosulfonyl)benzoate dissolved in 35-45 ml of THF, was added to the dilithiated intermediate, and the solution was stirred at room temperature under nitrogen overnight (16-18 hr.). Then 100 ml of 6 *M* hydrochloric acid was added, and the two-phase mixture was poured into a large flask containing ice (*ca.*, 100 g) followed by 100 ml of solvent grade ether or THF. The mixture was then neutralized with solid sodium bicarbonate and the layers separated. The aqueous layer was extracted with ether or THF (2 x 75 ml), and the organic fractions were combined, evaporated, and the solid was recrystallized from benzene/ethanol or xylenes/DMF.

Benzoisothiazolo[1,2-*b*][1,2]isoquinolin-11-one-1,1-dioxide (**1**).

This compound was prepared by the condensation-cyclization of dilithiated 2-methylbenzoic acid with the lithiated methyl 2-(aminosulfonyl)benzoate and/or lithiated saccharin: 96%, mp 319-321° (benzene/ethanol); IR ($cm^{-1}$): 1667, 1320, 1172; $^1H$ NMR ($CF_3COOD$) δ (ppm): 7.75 (s, 1H), 8.01-8.18 (m, 3H), 8.26-8.32 (m, 2H), 8.38-8.43 (m, 2H), 8.83 (d, 1H); $^{13}C$ NMR ($CF_3COOD$) δ (ppm): 107.5, 111.7, 119.2, 122.9, 124.8 (2), 127.8, 129.2, 130.9, 132.3, 133.5, 134.7, 138.4, 140.1, and 165.4.

*Anal.* Calcd. for $C_{15}H_9NO_3S$: C, 63.59; H, 3.20; N, 4.94. Found: C, 63.48; H, 3.15; N, 4.86.

6-Phenylbenzoisothiazolo[1,2-*b*][1,2]isoquinolin-11-one-1,1-dioxide (**2**).

This compound was prepared by the condensation-cyclization of dilithiated 2-(phenylmethyl)benzoic acid with the lithiated methyl 2-(aminosulfonyl)benzoate and/or lithiated saccharin: 62%, mp 324-327°(benzene/ethanol); IR ($cm^{-1}$): 1668, 1351, 1184; $^1H$ NMR ($CF_3COOD$) δ (ppm): 6.63 (d, 1H), 7.35 (t, 1H), 7.47 (s broad, 3H), 7.62 (t, 1H), 7.71 (s broad, 4H), 7.79 (t, 1H), 7.96 (d, 1H), and 8.56 (d, 1H); $^{13}C$ NMR ($CF_3COOD$) δ (ppm): 110.7, 114.4, 118.1, 121.9, 123.6, 126.4, 127.5, 129.1, 129.7, 131.3, 131.4, 131.5, 131.7, 132.7, 134.4, 136.7, 137.3, 141.0, and 164.1.

*Anal.* Calcd. for $C_{21}H_{13}NO_3S$: C, 70.18; H, 3.65; N, 3.90. Found: C, 70.07; H, 3.49; N, 3.81.

9-Methylbenzoisothiazolo[1,2-*b*][1,2]isoquinolin-11-one-1,1-dioxide (**3**).

This compound was prepared by the condensation-cyclization of dilithiated 2,5-dimethylbenzoic acid with the lithiated methyl 2-(aminosulfonyl)benzoate and/or lithiated saccharin: 50%, mp 307-310° (benzene/ethanol); IR ($cm^{-1}$): 1676, 1334, 1189; $^1H$ NMR ($CF_3COOD$) δ (ppm): 2.73 (s, 3H), 7.49 (s, 1H), 7.82-7.90 (m, 4H), 8.04 (t, 1H), 8.17 (d, 1H), and 8.42 (s, 1H); $^{13}C$ NMR ($CF_3COOD$) δ (ppm): 23.2, 107.5, 111.6, 115.3, 119.0, 122.8, 124.6, 124.7, 128.3, 130.7, 130.8, 133.9, 134.5, 138.2, 140.3, and 165.4.

*Anal.* Calcd. for $C_{16}H_{11}NO_3S$: C, 64.63; H, 3.73; N, 4.71. Found: C, 64.36; H, 3.46; N, 4.60.

8-Methylbenzoisothiazolo[1,2-*b*][1,2]isoquinolin-11-one-1,1-dioxide (**4**).

This compound was prepared by the condensation-cyclization of dilithiated 2,4-dimethylbenzoic acid with the lithiated methyl 2-(aminosulfonyl)benzoate and/or lithiated saccharin: 60%, mp 325-330° (xylenes/DMF); IR ($cm^{-1}$): 1675, 1320, 1188; $^1H$ NMR ($CF_3COOD$) δ (ppm): 2.65 (s, 3H), 7.37 (s, 1H), 7.59-7.65 (m, 2H), 7.80-7.85 (m, 2H), 7.93-8.09 (m, 2H), and 8.40 (d, 1H); $^{13}C$ NMR ($CF_3COOD$) δ (ppm): 23.2, 107.5, 111.6, 115.3, 119.0, 122.8, 124.6, 124.7, 129.0, 130.7, 130.8, 132.0, 134.0, 134.5, 138.2, and 165.4 [13].

*Anal.* Calcd. for $C_{16}H_{11}NO_3S$: C, 64.63; H, 3.73; N, 4.71. Found: C, 64.39; H, 3.66; N, 4.83.

8-Methoxybenzoisothiazolo[1,2-*b*][1,2]isoquinolin-11-one-1,1-dioxide (**5**).

This compound was prepared by the condensation-cyclization of dilithiated 4-methoxy-2-methylbenzoic acid with the lithiated methyl 2-(aminosulfonyl)benzoate and/or lithiated saccharin: 73%, mp 323-326° (xylenes/DMF); IR ($cm^{-1}$): 1660, 1336, 1180; $^1H$ NMR ($CF_3COOD$) δ (ppm): 4.18 (s, 3H), 7.35-7.44 (m, 3H), 7.89 (t, 1H), 8.02 (t, 1H), 8.12 (t, 1H), 8.50 (d, 1H), and 8.56 (s, 1H); $^{13}C$ NMR ($CF_3COOD$) δ (ppm): 58.2, 107.4, 111.8, 113.2, 115.5, 119.3, 121.2 (2), 123.0 (2), 124.9, 133.4, 134.9, 138.5, 143.0, and 167.7.

*Anal.* Calcd. for $C_{16}H_{11}NO_4S$: C, 61.33; H, 3.54; N, 4.47. Found: C, 61.44; H, 3.17; N, 4.07.

10-Methylbenzoisothiazolo[1,2-*b*][1,2]isoquinolin-11-one-1,1-dioxide (**6**).

This compound was prepared by the condensation-cyclization of dilithiated 2,6-dimethylbenzoic acid with the lithiated methyl 2-(aminosulfonyl)benzoate and/or lithiated saccharin: 55%, mp 337-339° (xylenes/DMF); IR ($cm^{-1}$): 1673, 1339, 1185; $^1H$ NMR ($CF_3COOD$) δ (ppm): 2.90 (s, 3H), 7.21 (s, 1H), 7.40 (d, 1H), 7.53 (d, 1H), 7.67 (q, 1H), 7.82 (t, 1H), 7.92 (m, 2H), and 8.38 (s, 1H); $^{13}C$ NMR ($CF_3COOD$) δ (ppm): 23.9, 106.9, 110.7, 114.4,

118.2, 121.9, 123.5, 125.1, 128.3, 130.8, 132.6, 136.5, 137.1, 140.5, 145.8, and 166.5. See also: ORTEP diagram, Figure 2, and Tables 1-3.

*Anal*. Calcd. for $C_{16}H_{11}NO_3S$: C, 64.63; H, 3.73; N, 4.71. Found: C, 64.37; H, 3.72; N, 4.81.

8-Methylbenzoisothiazolo[1,2-*b*][1,2]isoquinolin-11-one-1,1-dioxide (**7**).

This compound was prepared by the condensation-cyclization of dilithiated 2,3-dimethylbenzoic acid with the lithiated methyl 2-(aminosulfonyl)benzoate and/or lithiated saccharin: 75%, mp 363-365° (xylenes/DMF); IR ($cm^{-1}$): 1674, 1345, 1190; $^1H$ NMR ($CF_3COOD$) δ (ppm): 2.95 (s, 3H), 7.79-7.84 (m, 2H), 7.95-8.00 (m, 2H), 8.13 (t, 1H), 8.22 (d, 1H), 8.30 (d, 1H), and 8.56 (d, 1H). $^{13}C$ NMR ($CF_3COOD$) δ (ppm): 20.3, 104.3, 111.6, 115.4, 119.1, 122.9, 124.6, 124.8, 128.9, 132.1, 134.6, 138.3, 139.2, 139.6, and 165.4.

*Anal*. Calcd for $C_{16}H_{11}NO_3S$: C, 64.63; H, 3.73; N, 4.71. Found: C, 64.28; H, 3.39; N, 4.65.

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REFERENCES AND NOTES

[1] M. Baumgarth, N. Beier and R. Gericke, *J. Med. Chem*., **40**, 2017 (1997).

[2] T. S. Guion, M. U. Koller, R. J. Lachicotte, R. N. Rutledge, K. C. Hildebran, P. H. Le, and C. F. Beam, *Synth. Commun*., **26**, 1753 (1996).

[3] K. C. Hildebran, T. L. Cordray, K. W. Chan, and C. F. Beam, *Synth. Commun.*, **24**, 779 (1994).

[4] D. L. Comins and J. D. Brown, *J. Org. Chem.*, **51**, 3566 (1986).

[5] P. L. Creger, *J. Amer. Chem. Soc.*, **92**, 1396 (1970).

[6a] G. Boschin, A. D'Agostina, A. Arnoldi, E. Marotta, E. Zanardini, M. Negri, A. Valle, and C. Sorlini, *J. Environ. Sci. Health*, **B 38**, 737 (2003); [b] J. Rouchaud, O. Neus, H. Eelen and R. Bulcke, *Toxicol. Environ. Chem.*, **82**, 99 (2001); [c] B. S. Ismail and T.-V. Chong, *J. Oil Palm Res.* **13**, 1 (2001); [d] J. Rouchaud, O. Neus, and C. Moulard, *Internat. J. Environ. Anal. Chem.*, **79**, 65 (2001); [e] R. K. Juhler, S. R. Sorensen, and L. Larsen, *Water Res.*, **35**, 1371 (2001).

[7] S. P. Dunn, L. M. Hajiaghamohseni, S. B. Lioi, M. A. Meierhoefer, M. J. Walters and C. F. Beam, *J. Heterocyclic Chem*., **41**, 295 (2004).

[8] K. Goerlitzer and J. Weber, *Arch. der Pharmazie (Weinheim, Ger.)*, **31**, 76 (1981); *Chem. Abstr.*, **94**, 208740 (1981).

[9] Computer program, CrystalClear: Rigaku Corporation, Danvers, MA 01923, (1999).

[10] Computer program, teXsan for Windows version 1.06: Crystal Structure Analysis Package, Molecular Structure Corporation, The Woodlands, TX 77381-5209 (1997-9).

[11] D. T. Cromer and J. T. Waber, in International Tables for X-ray Crystallography, Vol. **IV**, The Kynoch Press, Birmingham, England, Table 2.2 A, (1974).

[12a] V. A. Shkulev, L. S. Abovyan, I. A. Dzhagatspanyan, N. E. Akopyan, and O. L. Mndzhoyan, *Khimiko-Farmatsevticheskii Zhurnal*, **13**, 36 (1979); *Chem. Abstr.*, **90**, 203623. (1979); [b] C. Olmedo, L. Deban, M. Coca, M. Vega, and F. De la Rosa, *Fresenius' J. Anal. Chem.*, **357**, 962 (1997); *Chem. Abstr.*, **127**, 1939 (1997); [c] C. P. Tseng, U.S. Patent US 4838925 A 19890613 (1989); *Chem. Abstr.*, **112**, 7508 (1989).

[13] Due to the limited solubility of all products, NMR spectra were taken with trifluoroacetic acid-*d*. This was the most challenging spectra (4784 scans), and the assignment was made by distinguishing the carbonyl absorption from trifluoroacetic acid absorptions.

[14a] D. C. Duncan, T. A. Trumbo, C. D. Almquist, T. A. Lentz, and C. F. Beam, *J. Heterocyclic Chem.*, **24,** 555 (1987); [b] C. L. Mazat, C. F. Beam, and M. A. Hines, *Synth. Commun.*, **20**, 253 (1990); [c] D. R. Hurst, K. L. French, A. J. Angel, A. R. Williams, M. E. Rampey, T. S. Guion, K. W. Chan, C. M. Kassis, S. L Studer-Martinez, and C. F. Beam *J. Heterocyclic Chem.*, **35**, 1357 (1998); [d] J. R. Downs, S. J. Pastine, D. A. Schady, H. A. Greer, W. Kelley, Jr., J. D. Townsend, and C. F. Beam, *J. Heterocyclic Chem.*, **38**, 691 (2001).

[15] D. T. Cromer., in International Tables for X-ray Crystallography, Vol. **IV**, Table 2.3.1, the Kynoch Press, Birmingham England, 1974. D. C. Creagh and W. J. McAuley, in International Tables for Crystallography, Vol **C**, A. J. C. Wilson, ed., Kluwer Academic Publishers, Boston, Table 4.2.6.8, (1992), pp. 219-222.