Preparation of spiro[Benzoisothiazole-Isoxazole] Dioxides from Dilithiated C(α),*O*-Oximes and Methyl 2-(Aminosulfonyl)benzoate

Bonnie J. Grant, Catherine R. Kramp, John D. Knight, Michelle A. Meierhoefer, Jarrett H. Vella, Carolyn L. Sober, Stephen S. Jones, Clyde R. Metz, and Charles F. Beam*

Department of Chemistry and Biochemistry, College of Charleston, Charleston, SC 29424

William T. Pennington and Donald G. VanDerveer

Department of Chemistry, Clemson University, Clemson, SC 29634

N. Dwight Camper

Department of Entomology, Soils, and Plant Diseases, Clemson University, Clemson, SC 29634

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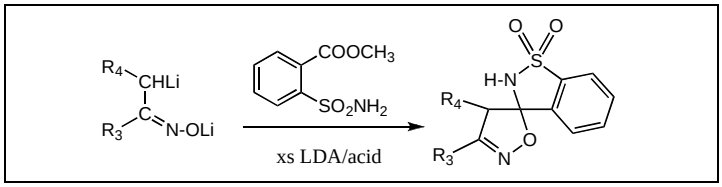

Several dilithiated C(α),O-oximes were prepared in excess lithium diisopropylamide-tetramethylethylenediamine (LDA/TMEDA) and condensed with methyl 2-(aminosulfonyl)benzoate followed by acid cyclization of intermediates to spiro(benzoisothiazole-isoxazole) dioxides, a new spiro and fused-ring system. Distortionless enhancement by polarization transfer (DEPT) and liquid chromatography mass spectrometry (LCMS) for all products, as well as X-ray single crystal analysis on a representative product, were especially relevant for structure confirmation in this synthesis.

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INTRODUCTION

Isoxazoles and 4,5-dihydroisoxazoles (2-isoxazolines) are well documented for their methods of preparation, their usefulness as synthetic intermediates, their biological potential and activity in both medicine and agriculture, and for varied spectral and theoretical studies [1]. They have also been a part of a spiroheterocyclic system with the spiro link atom between isoxazole and piperidine [2], isoxazole and indanone [3], isoxazole and flavanone (benzopyranone) [4], and isoxazole and isoxazole [5].

Benzoisothiazole dioxides, or 1,2-benzoisothiazole 1,1-dioxides (BIDs) have received less investigation regarding their synthesis and uses with many of these reports focused on their biological potential [6] in agriculture and medicine. A large part of the synthetic effort has focused on placing pendant groups in the 3-position with a few reports where BIDs have also been a part of a spiroheterocyclic system: spiro(BID-oxazolidine dione) [7], and spiro(BID-oxazolinone) [8].

We have found that methyl 2-(aminosulfonyl)benzoate **3** is especially useful for the synthesis of compounds containing a benzenesulfonamide or BIDS ring system, and such compounds have potential for agricultural use and biological activity [9]. In some instances this resulted when it has become an *ortho*-benzenesulfonamide pendant group of another molecule, usually a heterocycle [10].

One of our major synthetic endeavors has been the preparation of substituted isoxazoles [11] and pyrazoles [12] by employing strong base synthesis methods. Multiple anion-type intermediates, such as 1,4-dilithiated oximes **1**, or 1,4-dilithiated phenylhydrazones **2** have been used, beginning with readily available and inexpensive starting materials, such as substituted acetophenones and other C(α)-carbonyl compounds that are transformed into oximes and hydrazones, and also including a variety of electrophilic reagents such as substituted aromatic esters, aldehydes, and ketones.

Recently, we have been successful with carbanionic-nucleophile anionic-electrophile condensations where dilithiated intermediates of **1** or **2** were condensed-cyclized with lithiated methyl thiosalicylate [13], lithiated ethyl oxanilates [14], lithiated ethyl benzoylacetate [15], or lithiated methyl 2-(aminosulfonyl)benzoate. The utilization of the latter ester-sulfonamide **3** led to preparations of 3-benzoisothiazole dioxide-β-ketoesters [16] and benzoisothiazoloisoquinolinone dioxides, the latter being a new four fused ring heterocyclic system [17]. The ester-sulfonamide **3** has also been used in the preparation of pyrazolyl-*o*-benzenesulfonamides **4** [18] by the condensation of ester-sulfonamide **3** with dilithiated phenylhydrazone **2**, followed by acid cyclization of *C*-acylated intermediates to **4** instead of spiro(BID-pyrazole) **5**.

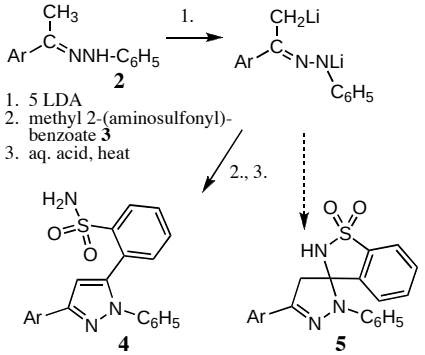

Figure 1. *N*-Phenyl-pyrazolyl-*o*-benzenesulfonamides.

We have also recently used tetramethylethylenediamine (TMEDA), a lithium chelating agent, in some of our synthetic endeavors when the original course of a reaction does not prove satisfactory. TMEDA can improve reaction yields, increase reaction rates, or even alter the course of a reaction. Systems involving LDA/TMEDA have given mixed results [19]. There is one account involving this complex and dilithiated β-ketoesters that is favorable, especially with regard to yield of products [20]. One of our initial projects involving the same type of dilithiated β-ketoester intermediates and ester-sulfonamide **3** usually improved the products yield or permitted the reaction to occur [16].

RESULTS AND DISCUSSION

During the current investigation, dilithiated C(α),*O*-oximes **1** of several substituted acetophenones (for **6-8**), 1-tetralones (for **9** and **10**), and cycloalkanones (for **11** and **12**), were prepared in excess LDA/TMEDA, condensed with methyl 2-(aminosulfonyl)benzoate **3**, and followed by acid cyclization of intermediates to give spiro(benzoisothiazole-isoxazole) **6-12** instead of isoxazolyl *o*-benzenesulfonamides **13** initially expected.

The new spiroheterocycles **6-12** were characterized by absorption spectra and an X-ray crystallographic analysis of spiro(BID-isoxazole)dioxide **7**. Its ORTEP diagram illustrated data obtained (Tables 1-3) which displays the spiro atom link between the two five-member rings, with the separate ring numbering, C5' of the isoxazole ring and C3 of the benzoisothiazole dioxide ring in **6-8**, and **11** and **12**; C3' and C3 in **9** and **10**. Clearly displayed DEPT spectra for **6-8** indicated a methylene carbon at the C4' position, δ 44.8-45.4 ppm, and spectra for **9-12** indicated a methyne carbon, also isoxazole C4' positions, δ 53.7-56.7 ppm. The DEPT was compared with the ^{13}C NMR to identify the spiro carbon atom in each product, and each displayed its ^{13}C NMR absorption in a narrow range, δ 96.2-97.6 ppm.

Products **7** and **8** had crystals that were free of incorporated solvents. Recrystallized products **6** and **9-12** contained solvent molecules. We have previously obtained products containing solvents included in the crystal, but not to the

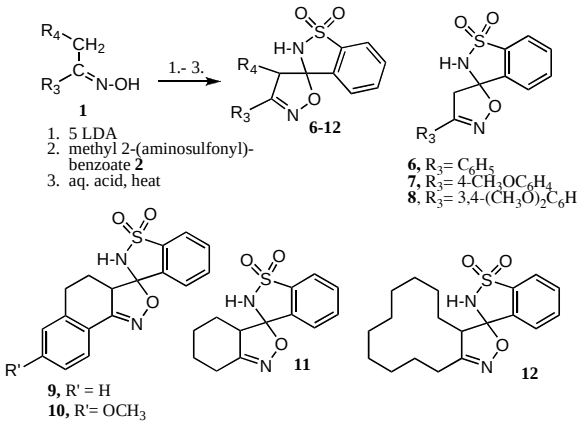

Figure 2. *spiro*(Benzoisothiazole-Isoxazole) Dioxides,**6-12.**

extent found in this study [16,18,21,22]. We also obtained liquid chromatographs with mass spectral detection (LCMS) for each product. In the positive mode, the expected $(M+H)^+$ molecular ion was found (see experimental).

A representative molecular structure from X-ray analysis for spiro(BID-isoxazole) **7** is shown in Figure 1. Atomic positional parameters are listed in Table 2, and selected bond distances and angles are listed in Table 3. Each molecule exhibits hydrogen bonding (refer to ORTEP diagram) between the H atom on the N2 nitrogen atom and the N1 nitrogen atom on a second molecule and between the N1 nitrogen atom and the hydrogen atom on the N2 nitrogen atom on a third molecule.

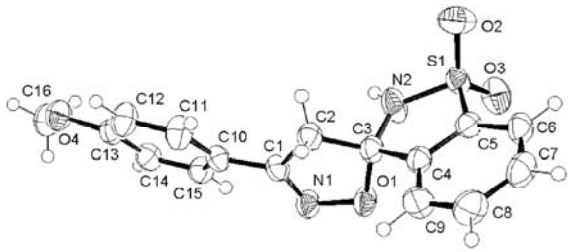

Figure 3. ORTEP diagram (50% ellipsoids for non-Hydrogen atoms) for **7**, $C_{16}H_{14}N_2O_4S$.

Energy calculations (B3YP/6-31G(d)) [23] were performed on representative products from **6-12** and **14** along with analogous isomers **4** and **5** from an earlier investigation [18]. The calculations indicate that **14** would be approximately 9 kcal mol^{-1} more stable than the spiro product(s) **6-12**, and **4** would be 14.7 kcal mol^{-1} more stable than **5**. While the heteroaromatic compounds **4** and **14** are more stable than their respective spiro isomers, **5** and **6-12**, spiroheterocycles **6-12** instead of **14** should be easier to prepare. In the earlier study [18] **4** was formed and not **5**, and the transformation of **4** to **5** in acid may be more difficult than the transformation of **14** to **6-12**.

Speculative mechanistic considerations may involve one of two, or both pathways, Claisen and aldol, and they are presented in a summary manner. Claisen path A:

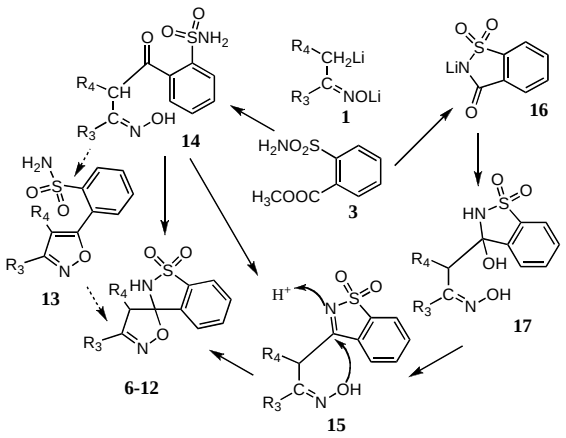

Figure 4. spiro(Benzoisothiazole-Isoxazole) Dioxides, Mechanism Considerations

1+3→14→15→6-12; Claisen path B: **1+3→14→13→6-12**; and aldol path: **3→16+1→17→15→6-12**. Two additional observations related to the mechanism were made without follow up investigation: (1) if saccharin was used instead of ester–sulfonamide **3**, no products were isolated. (2) Only a little more than a trace amount of saccharin was recovered when ester-sulfonamide **3** was treated with excess LDA under the same conditions employed for lithiation and condensation and acidification without reflux.

The yields of products ranged from 24-74 %, which may not be optimal for a given compound. Since TMEDA was used in this synthesis and not in the synthesis of pyrazolyl-*o*-benzenesulfonamides **4** [18], we can state that it was necessary for the overall success of the synthesis but further investigation may be necessary to determine its effect on the direction of the reaction. The reactions are regioselective, and multi-gram quantities of products can be obtained following recrystallization from common solvents. Since select pyrazolyl-*o*-benzenesulfonamides **4** have given astonishing results in an agricultural assay [24], the spiro(BID-isoxazole) **6-12** are undergoing related and appropriate biological testing.

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 and a Mattson Genesis II FT-IR with Specac Golden Gate Accessory. Nuclear magnetic resonance (NMR) spectra were obtained with a Varian Mercury-Vx spectrometer in an Oxford 300/54 magnet. Chemical shifts are recorded in δ (ppm) downfield from internal tetramethylsilane (TMS) reference. Combustion analyses were performed by Quantitative Technologies, Inc., P.O. Box 470, Salem Industrial Park, Bldg. 5, Whitehouse, NJ 08888.

LCMS analyses were measured on a Thermo-Finnigan LCQ Advantage system with the Surveyor autosampler, Surveyor pump, and LCQ Advantage Max mass spectral detector using electrospray ionization; 2-4 mg samples were prepared in 2 ml/l of acetonitrile; 10 µl injections were pumped at 1.00 ml/min isocratically with 70% acetonitrile and 30% water, each buffered with 0.1% formic acid by volume; 15 minute runs were reproduced in both the positive and negative MS modes. Data were collected at full scan from 100 to 650 amu.

General Procedure for the Preparation spiro(1,2-Benzoisothiazole–Isoxazole) 1,1-Dioxdes (6-12). 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, was added 49-50 ml of 1.6 *M* *n*-butyllithium (0.0788 mol) in hexanes (0°) under N_2. The flask was cooled in an ice water bath and 8.01 g (0.0788 mol) of diisopropylamine (99.5% - Aldrich Chem. Co.) dissolved in 25-30 ml of dry THF (freshly distilled from sodium) was added from the addition funnel at a fast drop rate during a 5 min (0°, N_2) period. The solution was stirred for an additional 15-20 min, and then treated *via* the addition funnel, during 5 min, with oxime [25] (0.015 mol) dissolved in 35-45 ml of THF. After 45-60 min, 7.36 g (0.063 mol) of TMEDA (99.5%) dissolved in 25 ml of THF was added, and the solution was stirred an additional 10-15 min Then, 45-60 min later, a solution of 3.47 g (0.0158 mol – 5% molar excess) of methyl 2-(aminosulfonyl)benzoate **3** dissolved in 25-35 ml of THF, was added over a period of 5 min, to the dilithiated intermediate **1**, and the solution was stirred overnight (room temp., N_2). Finally, 100 ml of 3 *M* hydrochloric acid was added all at once, followed by an additional 100 ml of solvent grade THF, and the two-phase mixture was well stirred and heated under reflux for approximately 45-60 min. At the end of this period, the mixture was poured into a large flask (*ca.* 1 or 2 liter) containing ice (*ca.*, 100 g), followed by the addition of 100 ml of solvent grade ether. The mixture was then neutralized with solid sodium bicarbonate, and the layers separated. The aqueous layer was extracted with ether (2x75 ml), and the organic fractions were combined, not dried, filtered, evaporated, and recrystallized to afford products.

3'-Phenyl spiro[1,2-benzoisothiazole-3,5'(4'*H*)-isoxazole] 1,1-dioxide (6). Compound **6** was prepared in 65% (3.01 g), mp 195-200° (ethanol/water) using the general procedure for the condensation-cyclization of dilithiated acetophenone oxime and ester-sulfonamide **3**; IR: 3500 cm^{-1}; ^1H NMR (deuteriochloroform, DMSO-d_6): δ 3.86 (d, 1H, CH, *J* = 17.1 Hz), 3.95 (d, 1 H, CH, *J* = 18.6 Hz), 7.44-7.47, 7.66-7.80, 8.01-8.03 (m, 9H, ArH), and 9.32 (s broad, NH); ^{13}C NMR (deuteriochloroform, DMSO-d_6): δ 45.1 (DEPT, CH_2), 96.4, 129.5, 124.3, 126.7, 128.6, 128.8 (2), 130.6, 131.3, 133.7, 136.6, and 157.1; LCMS, mw, 300.3; exact mass, 300.06: $(M+H)^+$, 300.9; $(M-H)^-$, 298.9. *Anal.* Calcd for $C_{15}H_{12}N_2O_3S•1/2H_2O$ [16b,18b,22b]: C, 58.24; H, 4.24; N, 9.05. Found: C, 58.35; H, 3.99; N, 8.67.

3'-(4-Methoxyphenyl) spiro[1,2-benzoisothiazole-3,5'(4'*H*)-isoxazole] 1,1-dioxide (7). Compound **7** was prepared in 74% (3.67 g), mp 195-201° (ethanol/benzene) using the general procedure for the condensation-cyclization of dilithiated 4'-methoxyacetophenone oxime and ester-sulfonamide **3**; IR: 3300 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.79 (d, 1H, *J* = 17.7 Hz, estimate), 3.82 (s, 3H), 4.19 (d, 1H, *J* = 17.7 Hz), 7.06 (d, 2H, *J* = 9.0 Hz), 7.36, 7.79-7.94 (m, 6H), and 9.58 (s broad, NH); ^{13}C NMR δ (DMSO-d_6): δ 45.4 (DEPT, CH_2), 56.1, 96.8, 115.1, 121.2, 121.8, 129.0 (2), 129.2, 132.3, 134.6, 137.0, 137.1, 157.7, and 161.7; LCMS, mw, 330.4; exact mass, 330.07: $(M+H)^+$, 330.9; $(M-H)^-$, 328.9. *Anal.* Calcd for $C_{16}H_{14}N_2O_4S$: C, 58.17; H, 4.27; N, 8.48. Found: C, 58.42; N, 4.31; N, 8.57.

Single crystal X-ray measurements for crystals of **7**, $C_{16}H_{14}N_2O_4S$ recrystallization from benzene and dimethylformamide (DMF) were collected on a Mercury CCD area detector coupled with

a Rigaku AFC8 diffractometer with graphite monochromated Mo-K (8 = 0.71073 Å) radiation. The data were collected a room temperature. Data was collected in 0.50° oscillations in ω with 30 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 27.1 mm. The detector swing angle was 0.00°. Cell parameters and additional details of the data collection are reported in Table 1.

Of the 12486 reflections collected, 2640 were unique (R_{int} = 0.0491); equivalent reflections were merged. Data were collected, processed, and corrected for Lorentz-polarization and for absorption using CrystalClear (Rigaku) [26]. The structures were solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Ideal hydrogen atom coordinates were calculated and the hydrogen atoms were allowed to ride on their respective carbons. The temperature factors of all hydrogen atoms were varied isotropically. The final cycle of full-matrix least-squares refinement on F^2 converged with R_1 = 0.0587 (reflections with $I > 2.00\Phi(I)$), wR_2 = 0.1574 (all data). The highest difference peak was 0.298 and the deepest hole was -0.326.

Structure solution, refinement, and the calculation of derived results were performed using the *SHELX-97* [27] package of computer programs. Neutral atom scattering factors were those of Cromer and Waber [28], and the real and imaginary anomalous dispersion corrections were those of Cromer [29].

Table 2

Atomic Positional Parameters for **7**, $C_{16}H_{14}N_2O_4S$

Atom	*x*	*y*	*z*	*U*(eq)*
S(1)	0.7056(1)	0.8229(1)	0.2456(1)	0.039(1)
O(1)	0.9098(2)	0.5387(3)	0.2332(1)	0.045(1)
O(2)	0.6427(2)	0.9656(3)	0.1971(2)	0.063(1)
O(3)	0.7322(2)	0.8150(3)	0.3452(2)	0.059(1)
O(4)	1.2567(2)	0.9273(3)	-0.0168(2)	0.050(1)
N(1)	1.0041(2)	0.5689(3)	0.2117(2)	0.042(1)
N(2)	0.8150(2)	0.7954(4)	0.2235(2)	0.057(1)
C(1)	0.9714(2)	0.6509(3)	0.1333(2)	0.036(1)
C(2)	0.8476(2)	0.6802(4)	0.0884(2)	0.041(1)
C(3)	0.8188(2)	0.6458(4)	0.1729(2)	0.038(1)
C(4)	0.7096(2)	0.5571(3)	0.1532(2)	0.037(1)
C(5)	0.6427(2)	0.6384(3)	0.1885(2)	0.037(1)
C(6)	0.5401(2)	0.5755(4)	0.1795(2)	0.045(1)
C(7)	0.5061(3)	0.4257(4)	0.1325(2)	0.054(1)
C(8)	0.5732(3)	0.3421(4)	0.0982(3)	0.057(1)
C(9)	0.6757(3)	0.4052(4)	0.1080(2)	0.049(1)
C(10)	1.0499(2)	0.7113(3)	0.0948(2)	0.036(1)
C(11)	1.0117(2)	0.7529(4)	-0.0016(2)	0.050(1)
C(12)	1.0836(3)	0.8213(5)	-0.0366(2)	0.050(1)
C(13)	1.1944(2)	0.8516(4)	0.0251(2)	0.039(1)
C(14)	1.2337(2)	0.8092(4)	0.1201(2)	0.042(1)
C(15)	1.1620(2)	0.7385(4)	0.1552(2)	0.041(1)
C(16)	1.3660(3)	0.9821(5)	0.0446(3)	0.059(1)

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

3'-(3,4-Dimethoxyphenyl)spiro[1,2-benzoisothiazole-3,5'-(4'*H*)-isoxazole] 1,1-dioxide (8). Compound **8** was prepared in 46% (2.41 g), mp 215-219° (ethanol/benzene) using the general procedure for the condensation-cyclization of dilithiated 3',4'-dimethoxyacetophenone oxime and ester-sulfonamide **3**; IR: 3367 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.71-3.86 (m, 7H), 4.19 (d, 1H, *J* = 18 Hz), 7.06-7.13, 7.26-7.34, 7.47, 7.55, 7.77-7.95, 8.19 (m, 7H), and 9.58 (s, broad, NH); ^{13}C NMR (DMSO-d_6): δ 44.8 (DEPT, CH_2), 55.6 (2), 96.2, 103.4, 109.1, 111.9, 119.6, 119.9, 120.6, 120.8, 125.0, 127.9, 130.7, 131.4, 131.6, 133.9, 142.3, and 157.2; LCMS, mw, 360.4; exact mass, 360.08: $(M+H)^+$, 360.9; $(M-H)^-$, 358.9. *Anal.* Calcd for $C_{17}H_{16}N_2O_5S$: C, 56.66; H, 4.47; N, 7.78. Found: C, 56.77; H, 4.26; N, 7.85.

1,2,3',4'-Tetrahydronaphth[1,2-*c*]-spiro[1,2-benzoisothiazole-3,3'(3a'*H*)-isoxazole] 1,1-dioxide (9). Compound **9** was prepared in 74% (3.87g), mp 142-146° (methanol/water) using the general procedure for the condensation-cyclization of dilithiated 1-tetralone oxime and ester-sulfonamide **3**; IR: 3332 cm^{-1}; ^1H NMR (deuteriochloroform, DMSO-d_6): δ 2.06-2.18 (m, 2H), 2.85-3.10 (m, 1H), 3.78-3.83 (m, 1H), 7.26-7.40, 7.67-7.82 (m, 7H), 7.99 (d, 1H, *J* = 6.9 Hz), and 9.00 (s broad, NH); ^{13}C NMR (deuteriochloroform, DMSO-d_6): δ 22.4 (DEPT, CH_2), 29.4 (DEPT, CH_2), 54.4 (DEPT, CH), 97.6, 120.9, 124.1, 124.9, 125.1, 126.9, 129.2, 131.0, 133.4, 136.0, 137.0, 139.1, and 157.5; LCMS, mw, 326.4; exact mass, 326.07: $(M+H)^+$, 327.0; $(M-H)^-$, 324.9. *Anal.* Calcd for $C_{17}H_{14}N_2O_3S•1/4CH_3OH•1H_2O$ [16b,22b]: C, 58.57; H, 4.84; N, 7.93. Found: C, 58.38; H, 4.48, N, 7.94.

7'-Methoxy-1,2,3',4'-tetrahydronaphth[1,2-*c*]spiro[1,2-benzoisothiazole-3,3'(3a'*H*)-isoxazole] 1,1-dioxide (10). Compound **10** was prepared in 57 % (3.32 g), mp 228-230° (methanol) using the general procedure for the condensation-cyclization of dilithiated 6-methoxy-1-tetralone oxime and ester-sulfonamide **3**; IR: 3543 cm^{-1}, sharp; ^1H NMR (deuteriochloroform): δ 2.00-2.12 (m,. 2H, CH_2), 2.90-2.98 (m, 2H, CH_2), 3.37 (s broad), 3.76-3.84 (m, 4H, CH and OCH_3), 6.76-6.87 (m, 2H, ArH), 7.67-7.91 (m, 5H, ArH), and 9.19 (s broad, NH). ^{13}C NMR (deuteriochloroform): δ 22.3 (DEPT, CH_2), 29.7 (DEPT, CH_2), 49.8, 54.4 (DEPT, CH_2), 55.3, 97.3, 113.2, 113.9, 117.4, 120.8, 124.2, 126.7, 131.3, 133.4, 135.9, 137.0, 141.2, 157.2, and 161.6; LCMS, mw, 356.4; exact mass, 356.08: $(M+H)^+$, 356.9; $(M-H)^-$, 354.9. *Anal.* Calcd for $C_{18}H_{16}N_2O_4S•CH_3OH$ [22b]: C, 58.90; H, 4.94 N, 7.23. Found: C, 58.69; H, 4.62; N, 7.28.

3',4'-Tetramethylenespiro[1,2-benzoisothiazole-3,5'(4'*H*)-isoxazole]1,1-dioxide (11). Compound **11** was prepared in 24 % (1.01 g), mp 192-196° (ethanol/water) using the general procedure for the condensation-cyclization of dilithiated cyclohexanone oxime and ester-sulfonamide **3**; IR: 3490 cm^{-1}; ^1H NMR (deuteriochloroform): δ 1.35-1.39 (m, 2H), 1.82-2.03 (m, 5H), 2.18-2.35 (m, 1H), 2.80-2.95 (m, 1H,), 3.34-3.40 (m, 1H), 5.69 (s broad, 1H), and 7.58-7.82 (m, 4H); ^{13}C NMR (deuteriochloroform): δ 24.2, 24.5, 25.4, 25.7, 56.7 (DEPT, CH), 97.5, 121.1, 124.1, 128.3, 131.2, 133.9, 137.9, and 161.1; LCMS, mw, 278.3; exact mass, 278.07: $(M+H)^+$, 279.0. *Anal.* Calcd for $C_{13}H_{14}N_2O_3S•7/8H_2O$ [16b,18b,21b]: C, 53.08; H, 5.40; N, 9.53. Found: C, 53.25; H, 5.27; N, 9.13.

3',4'-Decamethylene spiro[1,2-benzoisothiazole-3, 5'(4'*H*)-isoxazole] 1,1-dioxide (12). Compound **12** was prepared in 55 % (2.99 g), mp 186-190° (ethanol/water) using the general procedure for the condensation-cyclization of dilithiated cyclododecanone oxime and ester-sulfonamide **3**; IR: 3144 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.04-1.72 (m, 15 or 16H), 2.25-2.33 (m, 1H), 2.45-2.54 (m, 1H), 3.42-3.45 (m, 1H), 7.71-7.97 (m, 3H), and 9.40 (s broad, NH). ^{13}C NMR (DMSO-d_6): δ 21.9, 22.2, 22.9, 23.3, 23.5, 23.7, 23.8, 24.1, 25.7, 40.1, 40.3, 53.7 (DEPT, CH), 97.4, 120.6, 124.6, 131.6, 133.7, 135.8, 136.4, and 163.3; LC-MS, mw, 362.5; exact mass, 362.17: $(M+H)^+$, 363.1. *Anal.* Calcd for $C_{19}H_{26}N_2O_3S•1/2H_2O$ [16b,18b,21b]: C, 61.43; H, 7.33; N, 7.54. Found: C, 61.12; H, 7.01; N, 7.47.

Table 3

Selected Bond Distances (Å) and Angles (E) for **7**, $C_{16}H_{14}N_2O_4S$

S(1)-O(3)	1.423(2)
S(1)-O(2)	1.429(2)
S(1)-N(2)	1.621(3)
S(1)-C(5)	1.748(3)
N(2)-C(3)	1.444(4)
C(2)-C(3)	1.521(4)
O(1)-C(3)	1.451(3)
C(3)-C(4)	1.514(4)
C(4)-C(5)	1.374(4)
C(5)-C(6)	1.389(4)
C(6)-C(7)	1.380(5)
C(7)-C(8)	1.376(5)
C(8)-C(9)	1.386(5)
C(4)-C(9)	1.385(4)
O(1)-N(1)	1.427(3)
N(1)-C(1)	1.281(4)
C(1)-C(2)	1.496(4)
C(1)-C(10)	1.467(4)
C(10)-C(11)	1.393(4)
C(11)-C(12)	1.380(4)
C(12)-C(13)	1.388(4)
C(13)-C(14)	1.373(4)
C(14)-C(15)	1.386(4)
C(10)-C(15)	1.392(4)
O(4)-C(13)	1.374(3)
O(4)-C(16)	1.420(4)
O(3)-S(1)-O(2)	115.2(2)
O(3)-S(1)-N(2)	112.1(2)
O(2)-S(1)-N(2)	111.8(2)
O(3)-S(1)-C(5)	110.8(2)
O(2)-S(1)-C(5)	111.8(1)
N(2)-S(1)-C(5)	93.1(1)
C(3)-N(2)-S(1)	117.3(2)
N(2)-C(3)-O(1)	110.8(2)
N(2)-C(3)-C(4)	105.0(2)
O(1)-C(3)-C(4)	107.8(2)
N(2)-C(3)-C(2)	112.6(3)
O(1)-C(3)-C(2)	102.9(2)
C(4)-C(3)-C(2)	117.7(2)
N(1)-O(1)-C(3)	108.2(2)
C(1)-N(1)-O(1)	108.8(2)
N(1)-C(1)-C(2)	113.0(2)
C(1)-C(2)-C(3)	100.6(2)
C(4)-C(5)-S(1)	110.8(2)
C(7)-C(6)-C(5)	117.4(3)
C(8)-C(7)-C(6)	120.5(3)
C(7)-C(8)-C(9)	121.7(3)
C(4)-C(9)-C(8)	118.2(3)
C(5)-C(4)-C(9)	119.6(3)
C(9)-C(4)-C(3)	126.6(3)
C(5)-C(4)-C(3)	113.8(2)
C(4)-C(5)-C(6)	122.6(3)
C(6)-C(5)-S(1)	126.6(2)
N(1)-C(1)-C(10)	122.2(2)
C(10)-C(1)-C(2)	124.8(2)
C(11)-C(10)-C(1)	120.4(2)
C(12)-C(11)-C(10)	120.6(3)
C(11)-C(12)-C(13)	119.7(3)
C(14)-C(13)-C(12)	120.4(3)
C(13)-C(14)-C(15)	120.0(3)
C(14)-C(15)-C(10)	120.3(3)
C(15)-C(10)-C(11)	119.0(3)
C(15)-C(10)-C(1)	120.5(2)
C(14)-C(13)-O(4)	125.0(3)
O(4)-C(13)-C(12)	114.6(3)
C(13)-O(4)-C(16)	117.4(2)

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REFERENCES

[1a] Kanemasa, S. *Sci. Synth.* **2004** *19***,** 17. [b] Cicchi, S.; Cordero, F. M.; Giomi, D. *Prog. Heterocycl. Chem.* **2003** *15*, 261. [c] Boyd, G. V. *Prog. Heterocycl. Chem.* **1999**, *11***,** 213. [d] Boyd, G. V. *Prog. Heterocycl. Chem.* **1998**, *10***,** 209. [e] Sutharchanadevi, M.; Murugan, R.; Shinkai, I.. In *Comp. Heterocyclic Chem. II*, Ed. Elsevier, **1996**, *3*, 221, Oxford, UK [f] Broggini, G.; La Rosa, C.; Zecchi, G. *Synlett.* **1995**, 1208. [g] Bezborodov, V. S.; Kauhanka, N. N.; Lapanik, V. I.; Lee, C. J. *Liq. Cryst.* **2003**, *30*, 579. [h] Minkin, V. I.. *Chem. Rev.* **2004**, *104*, 2751.

[2] Fisera, L.; Sauter, F.; Froehlich, J.; Feng, Y.; Mereiter, K. *Monatsh. Chem.* **1994**, *125*, 909.

[3] El-Gendy, A. A.; Ahmedy, A. M. *Arch Pharm. Res.* **2000**, *23*, 310.

[4] Manikandan, S.; Jayashankaran, J.; Raghunathan, R. *Synth. Commun.* **2003**, *33*, 4063.

[5] Broggini, G.; Molteni, G.; Zecchi, G. *J. Org. Chem.* **1994**, *59*, 8271.

[6a] Wrobel, J.; Dietrich, A. *Heterocycles.* 1994, *38*, 1823. [b] D. O'Keefe, P.; Tepperman, J. M.; Dean, C.; Leto, K. J.; Erbes, D. L.; Odell, J. T. *Plant Physiol.* **1994**, *105*, 473.

[7] Wrobel, J.; Dietrich, A.; Woolson, S. A.; Millen, J.; McCaleb, M.; Harrison, M. C.; Hohman, T. C.; Sredy, J.; Sullivan, D. *J. Med. Chem.* **1992**, *35*, 4613.

[8] Wrobel, J.; Dietrich, A. U.S. Patent, 5,221,686, **1993**; *Chem. Abstr.* **1993**, *119***,** 180768.

[9a] Badon, R.; Bastide, J.; Sabadie, J. *Chemosphere.* **1990**, *21***,** 289. [b] Levitt, G. U.S. Patent, 4,339,267, **1982**; *Chem. Abstr.* **1982**, *98*, 215602.

[10a] Yoshida, H.; Shimano, S.; Konishi, K.; Mochizuki, S.; Koike, K.; Nakagawa, T. Japanese Patent, 62,161,761; *Chem. Abstr.* **1987**, *108*, 167298. [b] Sauers, R. F.; Shapiro, R.. British Patent, 2,112,784, **1983**; *Chem. Abstr.* **1983**, *100*, 6563. [c] Wolf, A. D.; Rorer, M. P. European Patent, 83,975. **1983**; *Chem. Abstr.* **1983**, *99*, 175812. [d] Hanagan, M. A. U.S. Patent, 4,604,131 **1986**; *Chem. Abstr.* **1986,** *106*, 45721. [e] E. I. du Pont de Nemours and Co. Japanese Patent, 61,280,491 **1986**; *Chem. Abstr.* **1986**, *106*, 102328.

[11] Fulmer, T. D.; Dasher, L. P.; Bobb, B. L.; Wilson, J. D.; Sides, K. L.; Beam, C. F. *J. Heterocyclic Chem.* **1999**, *17*, 799.

[12] Duncan, D. C.; Trumbo, T. A.; Almquist, C. D.; Lentz, T. A.; Beam, C. F. *J. Heterocyclic Chem.* **1987**, *24***,** 555.

[13] French, K. L.; Angel, A. J.; Williams, A. R.; Hurst, D. R.; Beam, C. F. *J. Heterocyclic Chem.* **1998**, *35*, 45.

[14] Downs, J. R.; Pastine, S. J.; Schady, D. A.; Greer, H. A.; Kelley, Jr, W.; Townsend, J. D.; Beam, C. F. *J. Heterocyclic Chem.* **2001**, *38*, 691.

[15] Livingston, M. J.; Chick, M. F.; Shealy, E. O.; Park, D. J.; Fulmer, T. D.; Beam, C. F. *J. Heterocyclic Chem.* **1982**, *19***,** 215.

[16] Meierhoefer, M. A.; Walters, M. J.; Dunn, S. P.; Vella, J. H.; Grant, B. J.; Sober, C. L.; Patel, N. S.; Hajiaghamohseni, L. M.; Lioi, S. B.; Metz, C. R.; Beam, C. F.; Pennington, W. T.; VanDerveer, D. G.; Camper, N. D. *J. Heterocyclic Chem.* **2006**, *43*, 307. [b] This ref.. compd. **11**: •1/2 H_2O

[17] Dunn, S. P.; Walters, M. J.; Metz, C. R.; Beam, C. F.; Pennington, W. T.; Krawiec, M. *J. Heterocyclic Chem.* **2004**, *41*, 1005.

[18] Meierhoefer, M. A.; Dunn, S. P.; Lioi, S. B.; Hajiaghamohseni, L. M.; Waltersm M. J.; Embree, M. C.; Grant, S. P.; Downs, J. R.; Townsend, J. D.; Metz, C. R.; Pennington, W. T.; Vanderveer, D. J.; Beam, C. F.; Camper, N. D. *J. Heterocyclic Chem.* **2005**, *42***,** 1095. [b] This ref. compd. **4g**: •3/4 H_2O

[19] Collum, D. B. *Acc. Chem. Res.* **1982**, *25*, 448.

[20] Narasimhan, N. S.; Ammanamanchi, R. *J. Org. Chem.* **1983**, *48*, 3945.

[21] Vella, J. H.; Patel, N. S.; Meierhoefer, M. A.; Hilton, E. J Sober, C. L.; Grant, B. J.; Metz, C. R.; Beam, C. F.; Pennington, W. T.; VanDerveer, D. G.; Camper, N. D. *J. Heterocyclic Chem.* **2006**, *43*, 315. [b] this ref., compd. **4**: 1/4 H_2O

[22] Downs, J. R.; Pastine, S. J.; Townsend, J. D.; Greer, H. A.; Kelley, Jr., W.; Schady, D. A.; Metz, C. R.; Almquist, C. D.; Pennington, W. T.; Bailey Walsch, R. D.; Lentz McConaughy, T. A.; Beam, C. F. *J. Heterocyclic Chem.* **2001**, *38*, 695. [b] this ref., compd. **8**: •1 $(CH_3)_3COH$

[23] Computer Program, B3LYP/6-31G(d): Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; *et al.* Gaussian 03, Revision B.4, Gaussian, Inc., Pittsburgh, PA, **2003**.

[24] Abstract: Gum, J.; Lyles, D.; Camper, N. D.; Beam, C. F. "Antitumor Activity of Selected Derivatives of 2-(1-Phenyl-1*H*-Pyrazol-5-yl)benzenesulfonamides," *Bull. South Carolina Acad. Sci.* **2006**, *LXVIII*, 86.

[25] Shriner, R. L.; Hermann, C. K. F.; Morrill, T. C.; Curtin, D. Y.; Fuson, R. C. In *The Systematic Identification of Organic Compounds*, 7th Ed., John Wiley and Sons, New York, **1997**, p 323, modified proced.: 10 g of NH_2OH•HCl in 60 ml H_2O; add 40 ml of 10 % NaOH soln.; then 10 g of carbonyl compd. then enough EtOH to effect soln.; heat, stir and boil off EtOH until cloudy; cool, let sit and cryst. should occur within min.

[26] Computer program, *CrystalClear*: Rigaku Corporation, Danvers, MA 01923, **1999**. Absorption correction used *REQABS*, Version 1.1: Jacobson, R. A. Molecular Structure Corporation, **1998**.

[27] Sheldrick, G. M. *SHELX-97*, *Crystallographic Computing System – Windows Version*, Release 97-2, **1997**.

[28] Cromer, D. T.; Waber, J. T.; In *International Tables for X-ray Crystallography*, Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 B, **1974**.

[29] Cromer, D. T. In *International Tables for X-ray Crystallography*, Vol. IV, Table 2.3.1, The Kynoch Press, Birmingham England, **1974**.