The Preparation of 3-Substituted 1,2-Benzisothiazole 1,1-Dioxides from Lithiated Intermediates or Grignard Reagents and Methyl 2-(Aminosulfonyl)benzoate

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A polylithiated β-ketoester, β-diketone, or β-ketoamide was condensed-cyclized with lithiated methyl 2-(aminosulfonyl)benzoate, to afford new 3-substituted 1,2-benzisothiazole 1,1-dioxides. Some Grignard or organolithium reagents were also condensed-cyclized with methyl 2-(aminosulfonyl)benzoate to give 3-substituted 1,2-benzisothiazole 1,1-dioxides.

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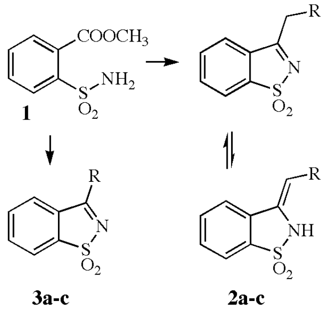
Benzisothiazole dioxides (1,2-benzisothiazole 1,1-dioxides - BIDs), especially 3-substituted, have been the focus of numerous studies [1] involving their preparation and use as synthetic intermediates [2], or for their biological potential in medicine and agriculture, and for spectral and other studies [3]. One synthetic method germane to this report is the condensation of pseudosaccharin chloride (3-Cl-BID) or saccharin (1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide) salts (usually metallic cation other than magnesium) with Grignard or organolithium reagents, where several alkyl and aryl pendant groups were introduced [4] into the 3-position.

Methyl 2-(aminosulfonyl)benzoate **1** has been an important compound for the synthesis of agriculturally significant products [5], where most of its reactions have involved the sulfonamide group. It has been transformed into saccharin and saccharin derivatives, used in spectral studies, and along with some of the agricultural products made from it, and has undergone environmental studies [6]. Reactions of **1** with bases have been used to make derivatives with the sulfonamide group, and hydrolysis studies have accompanied similar studies involving its agricultural products [7].

The preparation and reactions of select β-ketoester, β-diketone and β-ketoamide polyanions have been investigated including their condensation with aromatic esters [8]. Recently, the condensations of trilithiated acetoacetanilides with anionic electrophilic reagents, such as lithiated methyl salicylates or methyl thiosalicylate, followed by acid cyclization of *C*-acylated intermediates to 2-chromoneacetamides or 2-thiochromoneacetamides have been reported [9].

During this preliminary study, a β-ketoester (for **2 a**), a β-diketone (for **2 b**) and a β-ketoamide (for **2c**) were dilithiated (for **2a** and **2b**) or trilithiated (for **2 c**) with excess lithium diisopropylamide (LDA), followed by condensation with **1** to give intermediates that were not isolated but cyclized directly to BIDs (**2 a - c**), which are 3-substituted with β-ketoester (in **2 a**), β-diketone (in **2 b**), or β-ketoamide (in **2 c**) pendant groups. Sulfonamide ester **1** was also condensed-cyclized with some Grignard and organolithium reagents to afford 3-substituted BIDs (**3 a-c**).



2a R = CO-CH$_2$COOCH(CH$_3$)$_2$
2b R = CO-CH$_2$-CO-C$_6$H$_5$
2c R = CO-CH$_2$-CO-NHC$_6$H$_5$
3a R = CH$_3$
3b R = CH$_3$CH$_2$
3c R = C$_6$H$_5$

The experimental parameters for the preparation of **2a-c** are of particular importance. For BIDs **2a** and **2b**, a relative standard formation of dianion in excess LDA (substrate:LDA:ester-sulfonamide **1**, 1:5:1, THF solvent, 0°, N$_2$), with a 45-60 minute lithiation time. This is followed by addition of **1** to the dianions (in excess LDA), and then a three-hour condensation (all at 0°, N$_2$). In the case of the β-ketoamide, the time for trilithiation (extra equivalent of LDA, 1:6:1, β-ketoamide:LDA:ester) is three hours followed by an additional three-hour condensation time, usually at room temperature because of precipitate formation [9]. Under similar reaction conditions, only preparation of BID **2b** from lithiated **1** can be compared to the formation of the same compound(s) from saccharin, where the formation of compound(s) **2b** from **1** has given a better yield. The preparation of **3a-c** required the treatment of **1** with excess methyllithium, ethylmagnesium bromide, phenyllithium, or phenylmagnesium bromide (ester-sulfonamide:organometallic reagent, 1:3), followed by an overnight condensation at room temperature.

Neutralization of the mixture containing BIDs **2a** with cold dilute hydrochloric acid gave consistent results with other condensation-cyclizations using additional β-ketoesters currently under investigation. The procedure is being modified for **2b-c**, and related β-diketones and β-ketoamides. The latter materials for **2c** are presenting the greatest challenge and dilute acetic acid, or acetic acid/ammonium chloride, or saturated ammonium chloride solution is being used for neutralizations. In contrast, the condensations of the anionic electrophile from **1** with methyllithium, ethylmagnesium bromide, phenyllithium or phenylmagnesium bromide for **3a-c**, are quite straightforward, and only simple neutralization (saturated ammonium chloride) and ether extraction/evaporation of products is necessary.

The investigations involving compounds related to BIDs **2a-c** are at a different point relative to each other and to the completion of a particular project. There are subtle features being worked out for each study that are not immediately apparent from implementing what initially appears to be a general set of procedures described in detail in earlier related reports [9]. The condensation-cyclization involving the β-ketoester dianions with lithiated **1** is the most straightforward, followed by the condensations of this anionic electrophile from **1** with dilithiated β-diketones. Initial spectra review indicates that **2a** was a single N-*H*/ylidine tautomeric product; **2b** especially from ^{13}C NMR, indicated equal amounts of at least two N-*H*/ylidine tautomeric products, whose crystals were hydrated [10]; and **2c** is also predominantly a single N-*H*/ylidine tautomer, whose purified crystals were also hydrated.

The results bring up mechanistic considerations concerning the formation of **2a-c** and **3a-c**. The Grignard and organolithium reagents would deprotonate one of the sulfonamide hydrogens in **1**, followed by cyclization to saccharin, which would be deprotonated again to the lithium salt, that would condense with the third equivalent of the organometallic reagent to form **3a-c** [4]. Whether the same route is used for treatment of lithiated **1** with polylithiated β-keto intermediate in the presence of excess LDA is unclear. A Claisen-type condensation has occurred, with either *N*-lithiated **1** and/or *N*-lithiated saccharin, and they are possible intermediates.

The condensations of lithiated **1** with enolate systems, such as lithiated 2'-acetonaphthone, have given inconsistent results, and attempted condensations of lithiated **1** with dilithiated carboxylic acids, such as phenylacetic acid, have been unsuccessful.

We are developing the additional synthetic potential for the direct use of **1** beyond the preparation of BIDs **2a-c** and **3a-c** described here, which includes condensations of this anionic electrophile with other monoanion-type or polyanion-type systems.

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 magnetic resonance spectra were obtained with a Varian Associates Mercury Oxford 300 MHz NMR spectrometer, and chemical shifts are recorded in δ ppm downfield from an internal tetramethylsilane (TMS) standard. The GC-MS for **3c** was obtained with a Hewlett Packard 5971A MS/ 5890 Series III GC. Combustion analyses were performed by Quantitative Technologies, Inc., P.O. Box 470, Whitehouse, NJ 08888. The tetrahydrofuran (THF) was distilled from sodium (benzophenone ketyl as an indicator of dryness) prior to use, and organic chemicals were obtained from Aldrich Chemical Co. Lithium diisopropylamide (LDA) was prepared by a 1:1 reaction of 1.6 *M n*-butyllithium and diisopropylamine [9].

General Experimental Procedure for Preparation of 3-Substituted 1,2-Benzisothiazole 1,1-Dioxides (**2a-c**).

To a flask equipped with a nitrogen inlet tube, a side-arm addition funnel, and a magnetic stir bar, was added 0.079 mol LDA in 25-35 ml THF for **2a** and **2b** and 0.95 mol for **2c**. The β-ketoester, β-diketone or β-ketoamide (0.015 mol) was dissolved in 25-35 ml of THF for **2a** and **2b** and 50-60 ml THF for **2c** and stirred for 45-60 min for **2a** and **2b** and 2.5-3 hr for **2c**. This was followed by addition of 0.016 mol of methyl 2-(aminosulfonyl)-benzoate, dissolved in 40-50 ml of THF, and the solution was stirred and condensed for 2.5-3 hr (0°, nitrogen) for **2a,b** and room temperature for **2c**.

For BID **2a**, 100 ml of 3*N* hydrochloric acid was added quickly, and the two-phase mixture was well-stirred for 5-10 min, and partially neutralized with solid sodium bicarbonate (pH ~ 6-7). The mixture was poured into a large flask containing ice (*ca.*, 100 g), followed by the addition of 100 ml of solvent grade ether, extracted with ether (2x75 ml), and the organic fractions were combined, evaporated, and recrystallized. Crude yields are reported, and analytical melting points were obtained after a single recrystallization. Recovering a second crop was not attempted at this time.

(1-Methylethyl)-4-(1,1-dioxido-1,2-benzisothiazol-3(2*H*)-ylidine)-3-oxo-butanoate (**2a**).

Dilithiated isopropyl acetoacetate (0.015 mol, LDA: β-ketoester – 1:5) was condensed with lithiated **1** (0.0158 mol), followed by cyclization, addition of 100 ml of 3 *M* hydrochloric acid, extraction (2 X 50 ml) of ether, partial neutralization with sodium bicarbonate (pH~6-7), evaporation, and recrystallization to **2a**, in 90% yield, mp 151-153° (ethanol); ir: 3162 sh, 3093, 1723, 1656 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.28 (d, 6H, CH_3), 3.55 (s, 2H, CH_2), 5.09 (septet, 1H, CH), 6.21 (s, 1H, CH=), 7.27 (s, NH), 7.72-8.04 (m, 4H, ArH); ^{13}C nmr (deuteriochloroform): δ 21.7, 69.1, 90.3, 93.8, 121.4, 122.5, 128.4, 133.0, 133.3, 139.9, 146.2, 166.3, and 191.8.

When the same β-ketoester was treated with saccharin replacing **1** under a related set of reaction conditions **2a** was not isolated.

Anal. Calcd. for $C_{14}H_{15}NO_5S$: C, 54.36; H, 4.89; N, 4.53. Found: C, 54.32; H, 4.78; N, 4.47.

4-(1,1-Dioxido-1,2-benzisothiazol-3(2*H*)-ylidine)-1-phenylbutan-1,3-dione (**2b**).

Dilithiated 1-benzoylacetone (0.015 mol, LDA: β-diketone – 1:5) was condensed with lithiated **1** (0.0158 mol), followed by cyclization, addition of 100 ml of 3 *M* hydrochloric acid, extraction (2 X 50 ml) of ether, partial neutralization with sodium bicarbonate (pH~6-7), evaporation, and recrystallization was condensed and cyclized with the lithiated **1** to **2b**, in 87% yield, mp 221-223° (benzene/ethanol); ir: 3218, 3083, 1592 sh, 1379, 1152 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 6.42 (s,1H, CH), 6.65 (s, 1H, CH), 7.29 (s, 1H, NH), 7.36, 7.49-7.63 (m, 9H, ArH), 7.82-8.01, 8.06-8.15 (m, 9H, ArH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 95.3, 97.4, 106.6, 110.1, 112.8, 120.8, 122.7, 126.0, 126.8, 127.7, 128.4, 128.7, 129.2, 130.2, 130.7, 131.2, 131.9, 132.5, 133.5, 133.6, 145.4, 151.5, 153.8, 170.1, and 186.5.

When the same β-diketone was treated with saccharin (lithium salt) instead of **1** under a related set of reaction conditions (LDA: β-ketoester: saccharin, 3:1:1 or 4: 1: 1), **2b** was isolated in 16-18 % yield with the same tight melting point range, and its spectra were identical.

Anal. Calcd. for $C_{17}H_{13}NO_4S{\bullet}1/4H_2O$: C, 61.53; H, 4.10; N, 4.22. Found: C, 61.86, 61.65, H, 3.91, 3.87; N, 4.29.

N-Phenyl 4-(1,1-Dioxido-1,2-benzisothiazol-3(2*H*)-ylidine)-3-oxo-butanamide (**2c**).

Trilithiated acetoacetanilide (0.015 mol, LDA: β-ketoamide – 1:6) was condensed with lithiated **1** (0.0158 mol), followed by cyclization, addition of 100 ml of a 1:1 mixture of 3 *M* acetic acid and saturated ammonium chloride, extraction with (2 X 50 ml) of ether, evaporation, and recrystallization to **2c,** in 55% yield, mp 198-200° (ethanol); ir: 3231, 1648, cm^{-1}; ^1H nmr (dimethyl formamide): δ 3.33 (s broad, 2H, CH_2 and H_2O), 3.89 (s, 2H, CH_2), 5.72 (s broad, 1H, NH), 6.95-7.00 (m, 1H, CH), 7.21-7.26, 7.64-8.00 (m, 9H, ArH), and 10.88 (s broad, 1H, NH); ^{13}C nmr (dimethyl formamide): δ 51.9, 93.1, 119.4 (2), 120.6, 122.5, 123.0, 128.7 (2), 131.1, 131.9 (2), 140.3, 166.3, and 189.9.

When the same β-ketoamide was treated with saccharin instead of **1** under a related set of reaction conditions **2c** was not isolated.

Anal. Calcd. for $C_{17}H_{14}NO_4S{\bullet}2/3H_2O$: C, 57.62; H, 4.36; N, 7.90. Found: C, 57.29; H, 4.00; N, 7.82.

Preparation of 3-Substituted 1,2-Benzisothiazole 1,1-Dioxides (**3a-c**).

Ester-sulfonamide **1** (0.015 mol) in 25-35 mL of THF was treated directly with methyllithium, ethylmagnesium bromide, phenyllithium or phenylmagnesium bromide (0.047 mol) (RLi or PhMgBr: ester-sulfonamide, 3:1) at 0° and stirred at room temperature overnight followed by 100 ml saturated ammonium chloride solution, extraction (2 X 50 ml) with ether, evaporation and recrystallization to afford **3a,** (3-methyl-BID) in 83% yield, mp 210-214°; lit. mp 216-217° (benzene/ethanol) [4a,11]; **3b**, (3-ethyl-BID) in 29% yield, mp 132-134° (lit. mp 128.5-130.5°) (benzene/ethanol) [12]; and **3c,** (3-phenyl-BID) in 87% yield using phenyllithium and 31% yield using phenylmagnesium bromide, mp 160-162° (lit. mp 163-164°) (ethanol) [13] (GC-MS, M^+, 243, m/z, 179 (M-SO_2)).

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