The Preparation of 3-Substituted 1,2-Benzisothiazole-1,1-dioxides from the Condensation–Cyclization of Dilithiated β–Ketoesters with Methyl 2-(Aminosulfonyl)benzoate or 1,2-Benzisothiazol-3(2*H*)-one-1,1-dioxide

Michelle A. Meierhoefer, Matthew J. Walters, S. Patrick Dunn, Jarrett H. Vella, Bonnie J. Grant, Carolyn L. Sober, Nidhi S. Patel, Laela M. Hajiaghamohseni, Sara B. Lioi, Clyde R. Metz, and Charles F. Beam*

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

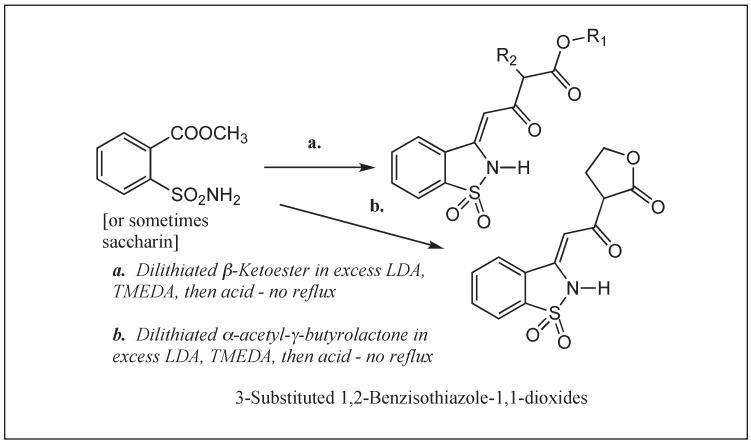
William T. Pennington and Donald G. VanDerveer

Department of Chemistry
Clemson University, Clemson, SC 29634

N. Dwight Camper

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

Received May 24, 2005



Several β-ketoesters were dilithiated with an excess of lithium diisopropylamide, followed by condensation with methyl 2-(aminosulfonyl)benzoate to give intermediates that were not isolated but cyclized to 3-substituted 1,2-benzisothiazole-1,1-dioxides. In most instances involving the ester-sulfonamide, a single β-ketoester tautomer is usually formed after recrystallization from ethanol. The same dilithiated β-ketoesters generally condense less well with 1,2-benzisothiazol-3(2*H*)-one-1,1-dioxide (saccharin) under the same conditions to afford the same products usually in the same or lower yields. The use of *N,N,N′,N′*-tetramethylethylenediamine during these syntheses has sometimes resulted in improved yields of products.

J. Heterocyclic Chem., **43**, 307 (2006).

Methyl 2-(aminosulfonyl)benzoate **1** is an important compound used for the synthesis of agriculturally significant products [1], where most of the preparative activity has involved the sulfonamide group. Many of the reactions involving the carbomethoxy ester group have dealt with its ability to form saccharin-related compounds. Saccharin **2** is a commercial sweetener [2] that also has synthetic uses [3].

Benzisothiazole-dioxides (BIDs) (1,2-benzisothiazole-1,1-dioxides) have been the focus of recent studies involving their preparation and use [4], especially as synthetic intermediates [5], or their potential for use in medicine [6], agriculture [7], and for spectral studies [8]. Three-substituted BIDs have received less investigation, possibly as a result of limited ways currently available to prepare them [5]. Two synthetic methods for 3-substituted BIDs germane to this report are the condensation of pseudosaccharin chloride 3 Cl-BID (3-chloro-1,2-benzisothiazole-1,1-dioxide), or saccharin **2** salts with Grignard or organolithium reagents [5c].

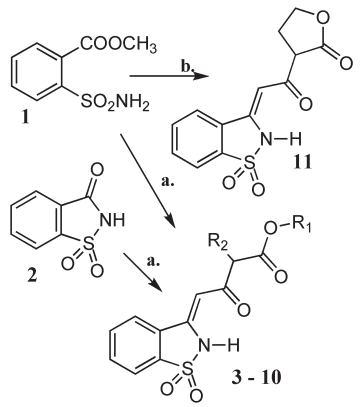
The preparation and reactions of select polylithiated β-ketoesters polyanion-type intermediates have been well studied [9], including their condensation with aromatic esters. Also, the use of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) during some of these syntheses has resulted in increased yields of products when routine esters, including ethyl benzoate, were used [10].

Other polylithiated β-ketoamides have also been investigated with regard to their condensation with anionic-electrophilic reagents, such as lithiated methyl salicylates or methyl thiosalicylate. The condensations were followed by acid catalyzed cyclization of *C*-acylated intermediates to 2-chromoneacetamides or 2-thiochromoneacetamides [11].

In an initial study, a single β-ketoester, isopropyl acetoacetate, was dilithiated and condensed with ester-sulfonamide **1**; condensations of these intermediates with saccharin **2** were inconsistent. Also, the effect of TMEDA had not been determined [12].

During this investigation several readily available β-ketoesters, such as methyl acetoacetate, were dilithiated with an excess of lithium diisopropylamide (LDA), followed by condensation with **1** [11] to give intermediates that were not isolated but cyclized directly to the 3-substituted BID products, **3-11**, with β-ketoester pendant groups. Each of the compounds is a solid, and they were isolated in 19-95 % yield from **1** and 22-86% yield (oils from **5**, **9**, and **11** did not afford crystalline products) from **2** after recrystallization from ethanol (benzene/ethanol for **10**). In most instances, using TMEDA improved the yield of product (*e.g.* for **9**, 46% without TMEDA and 95% with TMEDA). When saccharin **2** was used in place of ester-sulfonamide **1**, inconsistent results were obtained: BID **3** in higher yield; BIDs **4** and **8** in comparable yields; BIDs **6**, **7**, and **10** in lower yields; and while BIDs **5**, **9**, and **11**, readily prepared with **1** only gave oils in attempted preparations from **2**.

Scheme 1



a. *Dilithiated β-Ketoester in excess LDA, TMEDA, then acid - no reflux*

b. *Dilithiated α-acetyl-γ-butyrolactone in excess LDA, TMEDA, then acid - no reflux*

3. $R_1 = CH_3$, $R_2 = H$
4. $R_1 = CH_3CH_2$, $R_2 = H$
5. $R_1 = CH_2C_6H_5$, $R_2 = H$
6. $R_1 = CH_3$, $R_2 = CH_3CH_2$
7. $R_1 = CH_3CH_2$, $R_2 = CH_3CH_2$
8. $R_1 = (CH_3)_2CH$, $R_2 = H$
9. $R_1 = CH_3CH_2$, $R_2 = C_6H_5CH_2$
10. $R_1 = (CH_3)_3C$, $R_2 = CH_3CH_2$

3-BIDs/β-Ketoesters

The new products **3 – 11** were characterized by absorption spectra, X-ray crystal analysis (for **7** and **10**), with support from combustion analysis [13]. The spectra of products prepared usually indicated a single tautomer, which is in contrast to the spectra that can be obtained for the β-ketoester starting materials, usually a mixture of at least two tautomers. Infrared spectra for each compound displayed NH from 3171-3237 cm^{-1} along with carboxy and carbonyl absorptions from 1721-1766 and 1638-1676 cm^{-1} [5a]. The ^1H and ^{13}C NMR spectra were also consistent. Characteristic ^1H NMR absorptions for β-ketoester pendant groups were noted in the experimental (*e.g.,* ethoxy) with ^1H NMR and DEPT indicating methylene singlets ($-CH_2-$) from δ 3.48-3.62 ppm and methine singlets (CH=) from δ 6.14-6.53 ppm [5a]. The ^{13}C NMR absorptions for select carbons were readily identified: C-3 for the heterocyclic ring, δ 142.0-147.1 ppm; ethylene carbon (=CH), δ 92.8-94.3 ppm; β-keto-carbonyl, δ 190.0-194.7 ppm; methylene, δ 47.2-60.5 ppm; and ester carboxy, δ 166.8-173.2 ppm. X-ray analysis [14] of crystals of **7**, obtained from ethanol/benzene, and **10**, obtained from ethanol/hexanes, are the same tautomer described in the NMR spectral data for these products dissolved in deuteriochloroform. Purification of **10**, especially when prepared from **2**, offered the greatest challenge [13]. When either **1** or **2** were used, samples of **10** for satisfactory combustion analysis were prepared by recrystallization from benzene/ethanol instead of ethanol, and the expected tautomer, mp 276-280°, from **1** resulted. Another tautomer, mp 187-190°; resulted from **2**. When this latter tautomer was recrystallized without fragmentation [13], the melting point increased to 250-253°; its spectra were essentially identical to the tautomer prepared from **1** with the higher melting point. Also, a different solvent combination, ethanol/hexanes, was necessary to obtain satisfactory single crystals for X-ray analysis. The molecular structures of **7** and **10** from these analyses are shown in ORTEP diagrams, Figures 1 and 2, atomic positional parameters are listed in Table 2, and selected bond distances and angles are listed in Table 3.

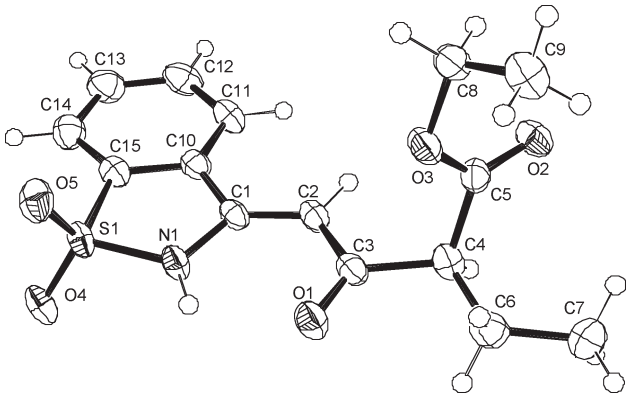


Figure 1. ORTEP diagram (50% ellipsoids for non-Hydrogen atoms) for $C_{15}H_{17}NO_5S$, BID/β-Ketoester **7**.

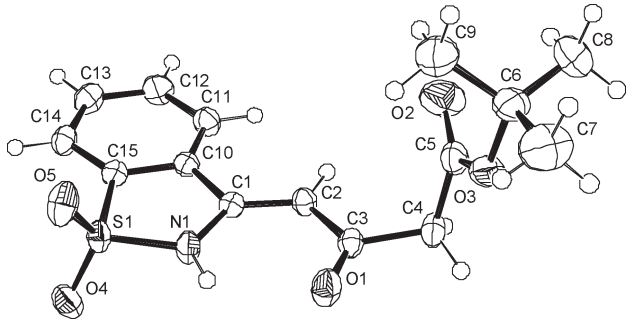


Figure 2. ORTEP diagram (50% ellipsoids for non-Hydrogen atoms) for $C_{15}H_{17}NO_5S$, BID/β-Ketoester **10**.

Table 1

Crystallographic Data for $C_{15}H_{17}NO_5S$

	BID/β-Ketoester **7**	BID/β-Ketoester **10**
Crystal Dimensions (mm)	0.48 x 0.24 x 0.10	0.70 x 0.16 x 0.16
Space Group	P-1	P1
a (Å)	7.917(2)	7.532(2)
b (Å)	8.587(2)	9.654(2)
c (Å)	12.286(3)	10.697(2)
α	107.41(3)°	81.17(3)°
β	102.86(3)°	82.39(3)°
γ	100.11(3)°	84.21(3)°
V (Å^3)	750.2(3)	759.3(3)
fw	323.36	323.26
Z	2	2
d_{calc} (g/cm^3)	1.431	1.414
μ (mm^{-1})	2.39	0.226
R_1 [a]	0.0481	0.0395
wR_2 [b]	0.1217	0.1038
Goodness of Fit	1.082	1.081

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

EXPERIMENTAL

Melting points were obtained with a Mel-Temp II melting point apparatus in open capillary tubes and are uncorrected [13].

Table 2

Atomic Positional Parameters, BID/β-Ketoester **7**

atom	x	*y*	*z*	*U*(eq)*
S(1)	0.1565(1)	0.1993(1)	0.9210(1)	0.029(1)
O(1)	0.4204(2)	0.3994(2)	0.7048(2)	0.035(1)
O(2)	0.9752(2)	0.3135(2)	0.7017(2)	0.038(1)
O(3)	0.6906(2)	0.1558(2)	0.6189(2)	0.036(1)
O(4)	0.527(2)	0.3076(2)	0.9696(2)	0.037(1)
O(5)	0.579(2)	0.336(2)	0.8383(2)	0.040(1)
N(1)	0.2949(2)	0.2923(3)	0.8632(2)	0.029(1)
C(1)	0.4742(3)	0.3031(3)	0.9098(2)	0.026(1)
C(2)	0.6055(3)	0.3530(3)	0.8643(2)	0.029(1)
C(3)	0.5706(3)	0.3977(3)	0.7586(2)	0.029(1)
C(4)	0.7350(3)	0.4486(3)	0.7181(2)	0.033(1)
C(5)	0.8175(3)	0.3015(3)	0.6819(2)	0.029(1)
C(6)	0.6888(4)	0.5113(4)	0.6139(2)	0.038(1)
C(7)	0.8535(4)	0.6036(5)	0.5922(3)	0.053(1)
C(8)	0.7517(3)	0.0084(3)	0.5644(2)	0.034(1)
C(9)	0.7809(4)	0.0083(4)	0.4478(2)	0.042(1)
C(10)	0.4973(3)	0.2500(3)	1.0147(2)	0.028(1)
C(11)	0.6547(3)	0.2519(4)	1.0937(2)	0.036(1)
C(12)	0.6421(4)	0.1941(4)	1.1861(3)	0.043(1)
C(13)	0.4781(4)	0.1349(4)	1.2008(3)	0.043(1)
C(14)	0.3197(4)	0.1319(3)	1.1233(2)	0.038(1)
C(15)	0.3348(3)	0.1916(3)	1.0320(2)	0.030(1)

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

Atomic Positional Parameters, BID/β-Ketoester **10**

Atom	*x*	*y*	*z*	*U*(eq)*
S(1)	0.1455(1)	0.2977(1)	0.4393(1)	0.027(1)
O(1)	0.4587(2)	-0.1047(1)	0.4326(2)	0.039(1)
O(2)	0.3780(2)	-0.2456(2)	0.1080(2)	0.058(1)
O(3)	0.6499(2)	-0.2958(2)	0.1787(1)	0.037(1)
O(4)	0.0951(2)	0.3169 (2)	0.5694(1)	0.040(1)
O(5)	0.2603(2)	0.3956(1)	0.3641(2)	0.041(1)
N(1)	0.2314(2)	0.1345(2)	0.4291(2)	0.030(1)
C(1)	0.1366(2)	0.0563(2)	0.3680(2)	0.023(1)
C(2)	0.1884(2)	-0.0760(2)	0. 3423(2)	0.025(1)
C(3)	0.3543(2)	-0.1526(2)	0.3752(2)	0.025(1)
C(4)	0.3995(3)	-0.2965(2)	0.3325(2)	0.032(1)
C(5)	0.4716(3)	-0.2773(2)	0.1929(2)	0.034(1)
C(6)	0.7558(3)	-0.2731(2)	0.0507(2)	0.042(1)
C(7)	0.9465(3)	-0.3000(4)	0.0823(3)	0.067(1)
C(8)	0.7111(4)	-0.3771(3)	-0.0295(2)	0.062(1)
C(9)	0.7197(4)	-0.1227(3)	0.0091(2)	0.058(1)
C(10)	-0.0287(2)	0.1397(2)	0.3327(2)	0.024(1)
C(11)	-0.1664(3)	0.0992(2)	0.2752(2)	0.032(1)
C(12)	-0.3084(3)	0.1967(2)	0.2476(2)	0.037(1)
C(13)	-0.3154(3)	0.3332(2)	0.2774(2)	0.035(1)
C(14)	-0.1808(2)	0.3748(2)	0.3362(2)	0.030(1)
C(15)	-0.0404(2)	0.2755(2)	0.3628(2)	0.024(1)

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

Fourier Transform infrared spectra were obtained with a Mattson Genesis II FT-IR with Specac Golden Gate Accessory. Proton and ^{13}C NMR spectra were obtained with a Varian Associates Mercury Oxford 300 MHz nuclear magnetic resonance spectrometer, which is approximately 75 MHz for ^{13}C NMR spectra. All NMR spectra were taken in deuteriochloroform solvent

Table 3
Selected Bond Distances (Å) and Angles (°)

BID/β-Ketoester **7**		BID/β-Ketoester **10**	
S(1)-O(4)	1.432(2)	S(1)-O(4)	1.428(2)
S(1)-O(5)	1.435(2)	S(1)-O(5)	1.427(2)
S(1)-N(1)	1.649(2)	S(1)-N(1)	1.655(2)
S(1)-C(15)	1.757(3)	S(1)-C(15)	1.759(2)
C(1)-N(1)	1.383(3)	C(1)-N(1)	1.376(2)
C(1)-C(10)	1.476(3)	C(1)-C(10)	1.473(2)
C(1)-C(2)	1.350(3)	C(1)-C(2)	1.356(2)
C(2)-C(3)	1.445(4)	C(2)-C(3)	1.443(3)
C(3)-O(1)	1.230(3)	C(3)-O(1)	1.224(2)
C(3)-C(4)	1.533(3)	C(3)-C(4)	1.521(2)
C(4)-C(5)	1.518(3)	C(4)-C(5)	1.510(3)
C(5)-O(2)	1.197(3)	C(5)-O(2)	1.207(3)
C(5)-O(3)	1.345(3)	C(5)-O(3)	1.328(2)
O(3)-C(8)	1.461(3)	O(3)-C(6)	1.488(2)
C(8)-C(9)	1.500(4)	C(6)-C(7)	1.507(3)
C(4)-C(6)	1.529(4)	C(6)-C(8)	1.506(4)
C(6)-C(7)	1.522(4)	C(6)-C(9)	1.507(3)
C(10)-C(11)	1.393(3)	C(10)-C(11)	1.390(3)
C(11)-C(12)	1.384(4)	C(11)-C(12)	1.383(3)
C(12)-C(13)	1.380(4)	C(12)-C(13)	1.397(3)
C(13)-C(14)	1.387(4)	C(13)-C(14)	1.384(3)
C(14)-C(15)	1.385(4)	C(14)-C(15)	1.382(3)
C(15)-C(10)	1.383(3)	C(15)-C(10)	1.389(2)
O(4)-S(1)-O(5)	116.3(1)	O(4)-S(1)-O(5)	116.6(1)
O(4)-S(1)-N(1)	111.5(1)	O(4)-S(1)-N(1)	110.6(1)
O(5)-S(1)-N(1)	110.3(1)	O(5)-S(1)-N(1)	110.4(1)
O(4)-S(1)-C(15)	112.2(1)	O(4)-S(1)-C(15)	112.2(1)
O(5)-S(1)-C(15)	111.7(1)	O(5)-S(1)-C(15)	112.1(1)
N(1)-S(1)-C(15)	92.1(1)	N(1)-S(1)-C(15)	92.4(1)
C(5)-O(3)-C(8)	116.9(2)	C(5)-O(3)-C(6)	121.4(2)
C(2)-C(1)-N(1)	124.6(2)	C(2)-C(1)-N(1)	125.4(2)
C(2)-C(1)-C(10)	126.0(2)	C(2)-C(1)-C(10)	125.3(2)
N(1)-C(1)-C(10)	109.4(2)	N(1)-C(1)-C(10)	109.3(1)
C(1)-N(1)-S(1)	115.3(2)	C(1)-N(1)-S(1)	115.7(1)
O(2)-C(5)-O(3)	123.8(2)	O(2)-C(5)-O(3)	125.9(2)
O(2)-C(5)-C(4)	124.7(2)	O(2)-C(5)-C(4)	123.7(2)
O(3)-C(5)-C(4)	111.4(2)	O(3)-C(5)-C(4)	110.4(2)
C(1)-C(2)-C(3)	122.6(2)	C(1)-C(2)-C(3)	123.5(2)
O(1)-C(3)-C(2)	123.1(2)	O(1)-C(3)-C(2)	122.6(2)
O(1)-C(3)-C(4)	121.2(2)	O(1)-C(3)-C(4)	120.0(2)
C(2)-C(3)-C(4)	115.7(2)	C(2)-C(3)-C(4)	117.3(2)
C(15)-C(10)-C(11)	118.8(2)	C(15)-C(10)-C(11)	118.9(2)
C(15)-C(10)-C(1)	111.9(2)	C(15)-C(10)-C(1)	112.7(2)
C(11)-C(10)-C(1)	129.2(2)	C(11)-C(10)-C(1)	128.5(2)
C(5)-C(4)-C(6)	109.0(2)	C(5)-C(4)-C(3)	108.9(2)
C(5)-C(4)-C(3)	110.8(2)	O(3)-C(6)-C(7)	102.3(2)
C(6)-C(4)-C(3)	112.0(2)	O(3)-C(6)-C(8)	109.6(2)
C(10)-C(15)-C(14)	123.3(2)	O(3)-C(6)-C(9)	109.3(2)
C(10)-C(15)-S(1)	110.5(2)	C(7)-C(6)-C(9)	110.6(2)
C(14)-C(15)-S(1)	126.2(2)	C(8)-C(6)-C(7)	111.9(2)
C(12)-C(11)-C(10)	118.6(2)	C(8)-C(6)-C(9)	112.6(2)
O(3)-C(8)-C(9)	110.6(2)	C(10)-C(15)-C(14)	123.5(2)
C(15)-C(14)-C(13)	116.9(3)	C(10)-C(15)-S(1)	109.8(1)
C(12)-C(13)-C(14)	120.9(3)	C(14)-C(15)-S(1)	126.7(1)
C(7)-C(6)-C(4)	113.1(2)	C(12)-C(11)-C(10)	118.7(2)
C(13)-C(12)-C(11)	121.5(2)	C(15)-C(14)-C(13)	116.8(2)
C(12)-C(13)-C(14)	121.0(2)		
C(13)-C(12)-C(11)	121.1(2)		

except **11**. 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. The tetrahydrofuran (THF) was distilled from sodium (benzophenone ketyl as an indicator of dryness) prior to use, and organic chemicals were obtained from Aldrich or Lancaster Chemical Co.

For the X-ray analyses, structure solution, refinement, and the calculation of derived results for **7** and **10** were performed using the *SHELX-97* [15] package of computer programs. Neutral atom scattering factors were those of Cromer and Waber [16], and the real and imaginary anomalous dispersion corrections were those of Cromer [17].

General Experimental Procedure for Preparing 3-Substituted 1, 2-Benzisothiazole-1,1-dioxides, **3-11**.

In a typical reaction sequence, LDA (0.079 mol) was prepared by the addition of 50 ml of 1.6 *M n*-butyllithium in hexanes (0.080 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 water bath and 8.14 g (0.080 mol) of diisopropylamine (99.5%) dissolved in 25-30 ml of THF was added from the addition funnel at a fast dropwise rate during a 5 min period (0°, nitrogen). The solution was stirred for an additional 15-20 min, and then rapidly treated with 0.015 mol of β-ketoester dissolved in 50 ml of dry THF, addition time 5 min. 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. This was followed by addition of 3.51 g (0.016 mol) of **1** (98%) or 2.99 g (0.016 mol) of **2** (98%), dissolved in 35 - 50 ml of THF, during 5 min, to the dilithiated intermediate, and the solution was stirred for 3.5 hr. (0°, nitrogen).

Finally, 150 ml of 3*M* hydrochloric acid was added quickly, the two-phase mixture was well stirred, and the mixture was poured into a large flask followed by the addition of 100 ml of solvent grade ether. The mixture was separated and the aqueous layer extracted with ether (2 X 75 ml). The organic layers were combined and extracted with 50 -75 ml of water. If a solid appeared at this point, the biphasic mixture could be filtered using a large Buchner funnel. The organic fractions were combined, evaporated, and recrystallized.

Methyl (1,1-Dioxido-1, 2-benzisothiazol-3(2*H*)-ylidine)-3-oxobutanoate (**3**) [from **1**, Methyl 2-(Aminosulfonyl)benzoate/from **2**, Saccharin].

This compound was prepared by the general procedure from the condensation-cyclization of 0.015 mol of methyl acetoacetate and 0.016 mol of **1** or **2** to yield 2.40 g (57 % from **1**) and 3.62 g (86 % from **2**), mp from **1** and **2**, 191-193° (ethanol) (**2** initial recrystallized mp 147-150° before additional recrystallizations [13]); IR (cm^{-1}): 3201, 1733, and 1662; ^1H NMR: 3.63 (s, 2H), 3.75 (s, 3H), 6.28 (s, 1H), 7.61 (s), and 7.79-7.93 (m, 4H); ^{13}C NMR: 47.8, 51.1, 93.7, 120.7, 122.2, 127.0, 132.4, 132.5, 132.9, 133.3, 146.4, 167.3, and 190.4.

Anal. Calcd for $C_{12}H_{11}NO_5S$: C, 51.24; H, 3.94; N, 4.98. Found: C, 51.20; H, 3.73; N, 5.01.

Ethyl (1,1-Dioxido-1, 2-benzisothiazol-3(2*H*)-ylidine)-3-oxobutanoate (**4**) [from **1**, Methyl 2-(Aminosulfonyl)benzoate/from **2**, Saccharin].

This compound was prepared by the general procedure from the condensation-cyclization of 0.015 mol of ethyl acetoacetate and 0.016 mol of **1** or **2** to yield 2.66 g (60 % from **1**), mp 150-153° (ethanol) and 2.92 g (66% from **2**); mp 151-153° (ethanol) from **2**; IR (cm^{-1}): 3174, 1729, and 1649; ^1H NMR: 1.30 (t, 3H), 3.60 (s, 2H), 4.22 (q, 2H), 6.22 (s, 1H), 7.29 and 7.73-7.90 (m, 4H, ArH); ^{13}C NMR: 14.3, 48.8, 61.8, 94.3, 121.9, 123.1, 128.9, 133.6, 133.9, 134.5, 146.7, 167.5, and 190.9.

Anal. Calcd for $C_{13}H_{13}NO_5S$: C, 52.87; H, 4.44; N, 4.74. Found: C, 52.73; H, 4.24; N, 4.70.

Phenylmethyl (1,1-Dioxido-1, 2-benzisothiazol-3(2*H*)-ylidine)-3-oxo-butanoate (**5**).

This compound was prepared by the general procedure from the condensation-cyclization of 0.015 mol of benzyl acetoacetate and 0.016 mol of **1** to yield 1.86 g, 19%, mp 128-130° (ethanol); condensation with **2** gave an oil; IR (cm^{-1}): 3203, 3168, 1734, and 1664; ^1H NMR: 3.62 (s, 2H), 5.21 (s, 2H), 6.14 (s, 2H), 7.26 (s), 7.34-7.39 (m, 5H), and 7.68-7.91 (m, 5H); ^{13}C NMR: 48.9, 67.5, 94.2, 122.0, 123.1, 128.4, 128.7, 128.8, 133.7, 133.9, 134.5, 135.4, 146.8, 167.3, and 191.2.

Anal. Calcd for $C_{18}H_{15}NO_5S$: C, 60.50; H, 4.23; N, 3.92. Found: C, 60.25; H, 4.15; N, 3.92.

Ethyl (1,1-Dioxido-1, 2-benzisothiazol-3(2*H*)-ylidine)-2-methyl-3-oxo-butanoate (**6**).

This compound was prepared by the general procedure from the condensation-cyclization of 0.015 mol of ethyl 2-methylacetoacetate and 0.016 mol of **1** or **2** to yield 2.90 g (65% from **1**), mp 128-130° (ethanol), and 1.74 g (39 % from **2**), mp 147-152° (ethanol); IR (cm^{-1}): 3177-3192, 1729, and 1652; ^1H NMR: 1.27 (t, 3H), 1.40 (d, 3H), 3.72 (q, 1H), 4.18 (q, 3H), 6.33 (s, 1H), 7.55, 7.80-8.09 (m, 4H); ^{13}C NMR: 12.5, 13.2, 51.4, 60.2, 92.8, 120.5, 122.2, 127.3, 132.5, 132.9, 133.6, 143.3, 169.5, and 194.0.

Anal. Calcd for $C_{14}H_{15}NO_5S \cdot 1/8\ H_2O$: C, 53.95; H, 4.93; N, 4.50. Found: C, 53.70; H, 4.40; N, 4.75.

Ethyl (1,1-Dioxido-1, 2-benzisothiazol-3(2*H*)-ylidine)-2-ethyl-3-oxo-butanoate (**7**).

This compound was prepared by the general procedure from the condensation-cyclization of 0.015 mol of ethyl 2-ethylacetoacetate and 0.016 mol of **1** or **2** to yield 2.86 g (59% from **1**), mp 131-133° (ethanol), and 1.91g (41 % from **2**), mp 128-130 ° (ethanol): IR (cm^{-1}): 3192, 1731, and 1655; ^1H NMR: 0.98 (t, 3H), 1.28 (t, 3H), 1.97-2.00 (m, 3H), 3.48 (t, 1H), 4.21 (q, 2H), 6.24 (s, 1H), 7.30(s), 7.75-7.89 (m, 4H); ^{13}C NMR: 12.0, 14.2, 22.7, 60.3, 61.6, 93.4, 121.8, 122.9, 129.0, 133.6, 133.5, 134.2, 146.8, 170.1, and 194.7.

Anal. Calcd for $C_{15}H_{17}NO_5S$: C, 55.72; H, 5.30; N, 4.33. Found: C, 55.95; H, 5.07; N, 4.28.

Single crystal X-ray measurements for crystals of **7**, $C_{15}H_{17}NO_5S$, recrystallized from warm benzene/ethanol [13] 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 -100 °C to a maximum θ value of 25.15°. Data were collected in 0.50° oscillations in ω with 45 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 6492 reflections collected, 2661 were unique (R_{int} = 0.0259); equivalent reflections were merged. Data were collected, processed, and corrected for Lorentz-polarization and for absorption using CrystalClear (Rigaku) [18]. 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 = 0.0481 (reflections with $I > 2.00\sigma(I)$), wR_2 = 0.1157 (all data). The highest difference peak was 0.470 and the deepest hole was -0.274.

1-Methylethyl (1,1-Dioxido-1, 2-benzisothiazol-3(2*H*)-ylidine)-3-oxo-butanoate (**8**).

This compound was prepared by the general procedure from the condensation-cyclization of 0.015 mol of isopropyl acetoacetate and 0.016 mol of **1** or **2** to yield 3.62 g (78% from **1**) and 3.43 g (74 % from **2**), mp from **1** and **2**, 151-153° (ethanol): IR (cm^{-1}): 3170, 1725, and 1655; ^1H NMR: 1.28 (d, 6H), 3.56 (s, 2H), 5.09 (septet, 1H), 6.22 (s, 1H), 7.29 (s), and 7.72-7.90 (m, 4H); ^{13}C NMR: 21.7, 49.0, 69.3, 94.2, 121.7, 122.9, 128.8, 133.4, 133.8, 134.3, 146.5, 166.8, and 191.5.

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.

Ethyl (1,1-Dioxido-1, 2-benzisothiazol-3(2*H*)-ylidine)-2-phenylmethyl-3-oxo-butanoate (**9**).

This compound was prepared by the general procedure from the condensation-cyclization of 0.015 mol of ethyl 2-benzylacetoacetate and 0.016 mol of **1** to yield 5.78 g (95%), mp 180-182° (ethanol); condensation with **2** gave an oil, IR (cm^{-1}): 3206, 1720, and 1668; ^1H NMR: 1.21 (t, 3H), 3.24-3.28 (m, 2H), 3.87 (t, 1H), 4.15 (q, 2H), 6.15 (s, 1H), 7.20-7.26, and 7.20-7.28, and 7.74-7.88 (m, 8H); ^{13}C NMR: 14.1, 34.7, 60.5, 61.7, 93.8, 121.8, 122.9, 126.8, 128.3, 128.6, 128.9, 133.5, 133.7, 134.3, 137.0, 146.5, 169.2, and 193.6. .

Anal. Calcd for $C_{20}H_{19}NO_5S$: C, 62.32; H, 4.97; N, 3.63. Found: C, 62.15; H, 4.77; N, 3.66.

1,1-Dimethylethyl (1,1-Dioxido-1, 2-benzisothiazol-3(2*H*)-ylidine)-3-oxo-butanoate (**10**).

This compound was prepared by the general procedure from the condensation-cyclization of 0.015 mol of *t*-butyl acetoacetate and 0.016 mol of **1** or **2** to yield 4.17 g and 1.07 g (from **1**, 86%, from **2**, 22%), mp (ethanol/benzene) **1**, 250-253° d; **2**, 187-190°; IR (cm^{-1}): from **1**, 3173; from **2**, 3529, 3482, **1**, 1723; **2**, 1692 and **1**, 1655, **2**, 1656; ^1H NMR: **1**, 1.49; **2**, 1.48 (s, 9H), **1**, 3.50; **2**, 3.36 (s, 2H), **1**, 6.20; **2**, 5.78 (s, 1H), **1**, 7.45; **2**, 7.43 (s), and **1**, 7.78 – 7.89; **2**, 7.57-7.83 (m, 4H); ^{13}C NMR: **1**, 28.1; **2**, 27.9, **1**, 50.1; **2**, 50.3, **1**, 82.5; **2**, 80.8, **1**, 94.3; **2**, 89.7, **1**, 122.0; **2**, 120.6, **1**, 123.0; **2**, 121.9, **1**, 129.1; **2**, 131.0, **1**, 133.6; **2**, 131.8, **1**, 133.9; **2**, 134.9, **1**, 134.7; **2**, 138.6, **1**, 147.1; **2**, 156.5, **1**, 166.7; **2**, 168.3, and **1**, 191.8; **2**, 188.8

From **1**: *Anal.* Calcd for $C_{15}H_{17}NO_5S$: C, 55.72; H, 5.30; N, 4.33. Found: C, 55.65; H, 5.11; N, 4.22.

From **2**: *Anal.* Calcd for $C_{15}H_{17}NO_5S$: C, 55.72; H, 5.30; N, 4.33. Found: C, 55.84; H, 5.13; N, 4.21.

Single crystal X-ray measurements for crystals of **10**, $C_{15}H_{17}NO_5S$, recrystallized from ethanol and hexanes [13] 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 -100 °C to a maximum θ value of 25.15°. Data were collected in 0.50° oscillations in ω with 45 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 6387 reflections collected, 2689 were unique (R_{int} = 0.0182); equivalent reflections were merged. Data were collected, processed, and corrected for Lorentz-polarization and for absorption using CrystalClear (Rigaku) [18]. 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 = 0.0395 (reflections with $I > 2.00\sigma(I)$), wR_2 = 0.1038 (all data). The highest difference peak was 0.279 and the deepest hole was -0.279.

2-(1,1-dioxido-1, 2-benzisothiazol-3(2H)-ylidene)-1-(dihydro-2-oxo-2(3*H*)-furan-3-yl)ethanone (**11**).

This compound was prepared by the general procedure from the condensation-cyclization of 0.015 mol of 3-acetyldihydro-2(3*H*)-furanone (α-acetyl-γ-butyrolactone) and 0.016 mol of **1** or **2** to yield 1.54 g (from **1**, 36%), mp 188-192° (ethanol); condensation with **2** gave an oil. IR (cm^{-1}): 1766, 1741 sh and 1637; ^{1}H NMR (deuteriochloroform): 2.43-2.52 (m, 1H), 2.81-2.90 (m, 1H), 3.87(q, 1H), 4.36-4.49 (m, 2H), 6.52 (s, 1H), 7.48 (s), and 7.78-7.96 (m, 4H); ^{13}C NMR (deuteriochloroform /DMSO-d_6): 24.1, 51.5, 67.2, 93.7, 121.2, 122.9, 128.3, 133.2, 133.7, 135.8, 144.5, 173.2, and 191.0.

Anal. Calcd for $C_{13}H_{11}NO_5S.1/2\ H_2O$: C, 51.65; H, 4.00; N, 4.63. Found: C, 51.94; H, 3.72: N, 4.99.

Acknowledgements.

We wish to thank the following sponsors: the National Science Foundation - Research at Undergraduate Institutions through grants CHE # 9708014 and # 0212699, and the United States Department of Agriculture, NRICGP # 2002-35504-12853. The assistance of Dr. Jason S. Overby is acknowledged with thanks.

REFERENCES AND NOTES

[1a] A. Thakur, M. Thakur, P. V. Khadikar, C. T. Supuran, and P. Sudele, *Bioorg. & Med. Chem.,* **12**, 789 (2004); [b] G. Boschin, A. D'Agostina, A. Arnold, E. Marotta, E. Zanardini, M. Negri, A.Valle, and C. Sorlini, *J. Environ. Sci. and Health, Part B: Pes., Food Contamin., Agr. Wastes*, **B38**, 737 (2003); [c] K. Chibale, J. Dauvergne, and P. G. Wyatt, *Synthesis,* 185 (2002); [d] J. Rouchaud, O. Neus, and C. Moulard, *Internat. J. Environ. Anal. Chem.,* **79**, 65 (2001); [f] I. Braschi, A. Pusino, C. Gessa, and J.-M. Bollag, *J. Ag. Food Chem.*, **48**, 2565 (2000); [g] Y. Xi, X. Wang, L. Kong, and L. Wang, *Pest. Sci.*, **55**, 751 (1999); [h] A. Vass, J. Dudas, and R. S. Varma, *Tetrahedron* Lett., **40**, 4951 (1999); [i] A. K. Bhattacherjee and P Dureja, *Pest. Sci*., **55**, 183 (1999).

[2] M. Naim, S. Nir, A. I. Spielman, A. C. Noble, I. Peri, S. Rodin, and M. Samuelov-Zubare, *ACS Sympos. Ser*., **825**, 2 (2002).

[3a] S. He, H. Yu, Q. Fu, R. Kuang, J. B . Epp, and W. C. Groutas, *Synth. Commun.*, **31**, 3055 (2001); [b] D. Dopp, P. Lauterfeld, M. Schneider, D. Schneider, G. Henkel, I. El Sayed, A. Yvette, and I. Elghamry, *Synth.*, 1228 (2001); [c] K. H. Ahn, H.-H. Baek, S. J. Lee, and C.-W. Cho, *J. Org. Chem.*, **65**, 7690 (2000); [d] K. H. Ahn, C. Ham, S.-K. Kim, C.-W. Cho, *J. Org. Chem.*, **62**, 7047 (1997); [e] A. Ahmed and H. Akhter, *J. Bangladesh Acad. Sci.*, **18**, 149 (1994); [f] D. J. Hlasta and J. H. Ackerman, *J. Org. Chem.*, **59**, 6184 (1994).

[4a] A. Siegemund, K.Taubert, and B. Schulze, *Sulfur Reports,* **23**, 279 (2002); [b] K Wojciechowski, *Heterocycles,* **57**, 1717 (2002); [c] H. Quiniou, and O. Guilloton, *Heterocyclic Chem.* **4,** 138 (1985); [d] A. De, *Prog. Med. Chem.,* **18**, 117 (1981).

[5a] R. A. Abramovitch, I. Shinkai, B. J. Mavunkel, K. M. More, S. O'Connor, G. H. Ooi, W. T. Pennington, P. C. Srinivasan, and J. R. Stowers, *Tetrahedron,* **52**, 3339 (1996). Related 3-substituted BIDs cited NH absorptions from 3180-3280 cm^{-1} along with analogous carbonyl (=CH-CO-) absorptions from 1650-1680 cm^{-1}. Analogous ^{1}H NMR spectra for (CH=) for a related compound, 3-benzoylmethylene-1,2-benzoisothiazoline-1,1-dioxide (2-(1,1-dioxido-1,2-benzisothiazol-3(2H)-ylidene)-1-phenylethanone, was noted at δ 6.82 ppm; [b] R. A. Abramovitch, K. M. More, I. Shinkai, and P. C. Srinivasan, *Heterocycles*, **5**, 95 (1976); [c] R. A. Abramovitch, E. M. Smith, M. Humber, B. Purtschert, P. C. Srinivasan, and G. M. Singer, *J. Chem. Soc., Perkin Trans. 1: Org. Bio-Org. Chem.*, 2589 (1974); [d] F. A. Davis, J. C. Towson, D. B. Vashi, R. ThimmaReddy, J. P. McCauley, Jr., M. E. Harakal, and D. J. Gosciniak, *J. Org. Chem.*, **55**, 1254 (1990); [e] A. Mustafa and M. K. Hilmy, *J. Chem. Soc.,* 1339 (1952).

[6a] Z. Kapui, M. Varga, K. Urban-Szabo, E. Mikus, S. Endre; S. Tibor, B. Judit, O. F. Sandor, and P. Aranyl, *J. Pharm. Exper. Thera.*, **305**, 451 (2003); [b] G. Gonzalez-Martin, C. Lyndon, and C. Sunkel, *Euro. J. Pharm. Biopharm.*, **46**, 293 (1998); [c] M. Abou-Gharbia, J. A. Moyer, U. Patel, M. Webb, G. Schiehser, T. Andree, and J. T. Haskins, *J. Med. Chem.*, **32**, 1024 (1989); [d] K. D. Combrink, H. B. Gulgeze, N. A. Meanwell, B. C. Pearce, P. Zulan, G. S. Bisacchi, D. G. Roberts, P. Stanley, and S. M. Seile, *J. Med. Chem.*, **41**, 4854 (1998); [e] C. E. Sunkel, M. Fau de Casa-Juana, L. Santos, A. G.Garcia, C. R. Artalejo, M. Villarroya, M. A. Gonzalez-Morales, M. G. Lopez, J. Cillero, S. Alonso, and S. A. Alter, *J. Med. Chem*., **35**, 2407 (1992).

[7a] K. Sakamoto,Y. Tada, Y Yokozeki, H. Akagi, N. Hayashi, T. Fujimura, and N. Ichikawa, *Plant Molec. Bio.*, **40**, 847 (1999); [b] M. Geiger, P. Walch-Liu, C. Engels, J. Harnecker, J. E.-D. Schulze, F. Ludewig, U. Sonnewald, W.-R. Scheible, and M. Stitt, *Plant, Cell Environ.,* **21**, 253 (1998); [c] M. Mor, F. Zani, P. Mazza, C. Silva, F. Bordi, G. Morini, and P. V. Plazzi, *Farmaco,* **51**, 493 (1996); [d] M. Uchiyama, H. Abe, S. Hiroshi, R. Sato, M. Shimura, and T. Watanabe, *Ag. Bio. Chem.,* **37**, 737 (1973); [e] K. Yoshioka, H. Nakashita, D. F. Klessig, and I. Yamaguchi I., *Plant J. : Cell Molec. Biol.,* **25**, 149 (2001); [f] Y. Miyamoto, Y. Ikeda, and K. Wakabayashi, *J. Pest. Sci.,* **28**, 293 (2003).

[8a] P. Naumov, G. Jovanovski, M. G. B. Drew, and S. W. Ng, *Inorg. Chim. Acta*, **314**, 154 (2001); [b] Y. I. Binev, C. T. Petkov, and L. Pejov, *Spectrochimica Acta, Part A: Molec. Biomol. Spect.,* **56A**, 1949 (2000); [c] P. Naumov and G. Jovanovski, *Spectrochim. Acta, Part A: Molecul. Biomolecul. Spec.*, **56A**, 1305 (2000); [d] L. Pejov, G. Jovanovski, O. Grupce, and B. Soptrajanov, *J. Molecul. Struct.*, **410-411,** 365 (1997); [e] W. Danikiewicz and K. Wojciechowski, *Euro. Mass Spec.,* **3**, 55 (1997); [f] O. Grupce, M. Penavic and G. Jovanovski, *J. Chem. Crystall.*, **24**, 581 (1994); [g] W. Danikiewicz, K. Wojciechowski, R. H. Fokkens, H. Roel, and N. M. M. Nibbering, *Org. Mass Spec.*, **28**, 853 (1993).

[9a] P. Langer and E. Bellur, *J. Org. Chem.*, **68**, 9742 (203); [b] Y. Chen and S. McN. Sieburth, *Synthesis,* 2191 (2002); [c] H. B. Jannet, A. A. Mourabit, A. Gateau-Olesker, C. Marazano, and Z. Mighri, *Tetrahedron: Asym.*, **10**, 2381 (1999); [d] B. Lygo, *Tetrahedron*, **51**, 12859 (1995); [e] B. Lygo and N. O'Connor, *Tetrahedron Lett.*, **28**, 3597 (1987) [f] P. Langer and E. Bellur, *J. Org. Chem.,* **68,** 9742 (2003); [g] I. Pevet, C. Meyer, and J. Cossy, *Tetrahedron Lett.*, **42**, 5215 (2001).

[10a] N. S. Narasimhan and R. Ammanamanchi, *J. Org. Chem.*, **48**, 3945 (1983); [b] M. Yamaguchi, K. Shibato, H. Nakashima, and T. Minami, *Tetrahedron,* **44**, 4767 (1988).

[11a] 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); [b] A. J. Angel, A. E. Finefrock, K. L. French, D. R. Hurst, A. R. Williams, M. E. Rampey, S. L. Studer-Martinez and C. F. Beam, *Can. J. Chem.*, **77,** 94 (1999); [c] J. R. Downs, S. P. Grant, J. D. Townsend, D. A. Schady, S. J. Pastine, M. C. Embree, C. R. Metz, W. T. Pennington, R. D. Bailey Walsch and C. F. Beam, *Can. J. Chem*., **82**, 659 (2004).

[12a] 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); [b] S. P. Dunn, M. J. Walters, C. R. Metz, C. F. Beam, and W. T. Pennington, *J. Heterocyclic Chem*., **41**, 1005 (2004).

[13] Repeated recrystallizations from ethanol could cause hydrolysis/cleavage of the β-ketoester pendant group and the isolation of saccharin.

[14a] D. Dopp, P. Lauterfeld, M. Schneider, D. Schneider, G. Henkel, I. El Sayed, A. Yvette and I. Elghamry, *Synthesis,* 1228 (2001); [b] I. Elghamry, D. Dopp, and G. Henkel, *Synthesis,* 1223 (2001).

[15] *SHELX-97 - Crystallographic Computing* 1997. G. M. Sheldrick, *SHELXTL*, *Crystallographic Computing System – Windows Version*, Release 97-2, Bruker Analytical X-Ray Systems: Madison, WI, (1997).

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

[17] D. T. Cromer in "International Tables for X-ray Crystallography," Vol. **IV**, table 2.3.1, the Kynoch Press, Birmingham England, (1974).

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