

An Odorless Preparative Method of Sulfides and Thiocarboxylic S-Esters Using 3-(Alkylthio)-1,2-benzisothiazole 1,1-Dioxide

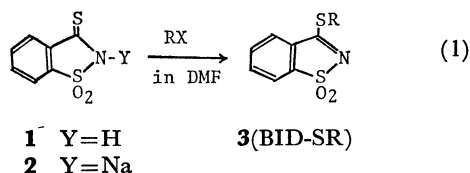
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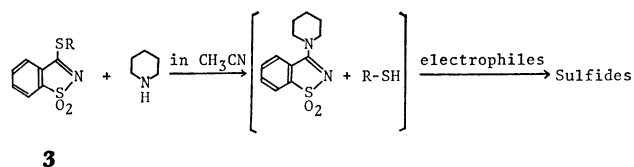
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Synopsis. It was found that sodium salt of 1,2-benzisothiazole-3(2H)-thione 1,1-dioxide (thiosaccharin) readily reacted with alkyl halide affording 3-(alkylthio)-1,2-benzisothiazole 1,1-dioxide (**3**). Treatment of **3** with piperidine produces the corresponding alkanethiol *in situ* quantitatively and subsequent treatment with various electrophiles gives the corresponding sulfides and thiocarboxylic S-esters in good yields.

Recently the herbicidal and fungicidal properties of 3-substituted 1,2-benzisothiazole 1,1-dioxide have been noted,^{1,2)} and the preparation of such compounds was performed by the reaction of 3-chloro-1,2-benzisothiazole 1,1-dioxide with an alcohol or thiol in the presence of base.²⁾ Generally, thiols have unpleasant odor, therefore the development of odorless equivalent of thiols would be convenient. We have found that 3-(alkylthio)-1,2-benzisothiazole 1,1-dioxide (**3**), which is prepared from the sodium salt (**2**) of thiosaccharin (**1**) and alkyl halides is an efficient synthetic equivalent of alkanethiols. 3-(Alkylthio)-1,2-benzisothiazole 1,1-dioxide (**3**) was prepared upon treatment of **2** with 1.1 equivalent of halide in excellent yields as shown in Table 1 (Eq. 1). Odorless compounds **3** reacted



with secondary amines stoichiometrically. The reaction of **3** with piperidine produces the corresponding alkanethiols smoothly *in situ*. Subsequently treatment with electrophiles gives the corresponding sulfides in one-pot reaction. Treatment with acid chlorides led



to the corresponding thiocarboxylic S-esters in high yields. In the same manner, the reactions with other electrophiles such as α,β -unsaturated carbonyl compounds, alkyl halides and epoxide also give satisfactory results. As mentioned above, it is clear that readily available **3** is a useful equivalent of the corresponding thiol.

Experimental

Preparation of 3-(Alkylthio)-1,2-benzisothiazole 1,1-Dioxides (3a–g). Typically, to a solution of **2** (663 mg, 3 mmol) in DMF (2 ml) was added a solution of benzyl bromide (564 mg, 3.3 mmol) in DMF (2 ml) at room temperature under nitrogen. After stirring for 3 h, water was

TABLE 1. PREPARATION OF 3-(ALKYLTHIO)-1,2-BENZISOTHIAZOLE 1,1-DIOXIDE (**3**) FROM THE SODIUM SALT (**2**) AND HALIDES

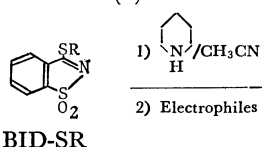
RX	Time/h	3a–g	Yield/%
PhCH ₂ Br ^{b)}	3	3a	93
PhCH ₂ CH ₂ Br ^{c)}	11	3b	82
PhCH=CHCH ₂ Cl ^{c)}	3.5	3c	84
CH ₂ =CHCH ₂ Br ^{b)}	3	3d	87
CH ₂ =C(CH ₃)Br ^{b)}	4	3e	80
N $\equiv$ CCH ₂ Cl ^{b)}	3.5	3f	85
CH ₃ I ^{b)}	3	3g	89

a) The reactions performed in DMF. b) Room temp. c) 50 °C.

added to the reaction mixture. The precipitate was recrystallized from ethanol and dichloromethane to give 3-(benzylthio)-1,2-benzisothiazole-1,1-dioxide (**3a**) (791 mg, 93%), whose structure was established by comparison with the authentic sample prepared by the reaction of 3-(chloro)-1,2-benzisothiazole 1,1-dioxide with benzenemethanethiol in the presence of triethylamine in CH₃CN (Mp, IR). **3a**: Mp 141.0–142.0 °C; IR (KBr) 1587, 1320, 1163 cm⁻¹; Found: C, 57.82; H, 3.94; N, 4.75%. Calcd for C₁₄H₁₁NO₂S₂: C, 58.11; H, 3.83; N, 4.85%. **3b**: Mp 144.5–145.5 °C; IR (KBr) 1587, 1312, 1163 cm⁻¹; Found: C, 59.34; H, 4.14, N, 4.75%. Calcd for C₁₅H₁₃NO₂S₂: C, 59.40; H, 4.32; N, 4.62%. **3c**: Mp 129.5–130.5 °C; IR (KBr) 1587, 1328, 1166 cm⁻¹; Found: C, 61.12; H, 4.31; N, 4.38%. Calcd for C₁₆H₁₃NO₂S₂: C, 60.93; H, 4.15; N, 4.44%. **3d**: Mp 114.0–115.0 °C; IR (KBr) 3067, 1497, 1325, 1235, 1167, 990, 930, 784 cm⁻¹; Found: C, 50.37; H, 3.81; N, 5.82%. Calcd for C₁₀H₇NO₂S₂: C, 50.19; H, 3.79; N, 5.86%. **3e**: Mp 168.0–169.0 °C; IR (KBr) 3257, 1493, 1319, 1157 cm⁻¹; Found: C, 50.63; H, 2.85; N, 5.73%. Calcd for C₁₀H₇NO₂S₂: C, 50.62; H, 2.97; N, 5.90%. **3f**: Mp 234.5–235.5 °C; IR (KBr) 2247, 1504, 1318, 1163 cm⁻¹; Found: C, 45.47; H, 2.30; N, 11.97%. Calcd for C₈H₆N₂O₂S₂: C, 45.39; H, 2.54; N, 11.76%. **3g**: Mp 227.5–228.5 °C; IR (KBr) 1488, 1316, 1170, 1156 cm⁻¹; Found: C, 45.30; H, 3.17; N, 6.53%. Calcd for C₈H₇NO₂S₂: C, 45.08; H, 3.31; N, 6.57%.

Preparation of Thiocarboxylic S-Esters (4a–h). Typically, to a solution of 3-(methylthio)-1,2-benzisothiazole 1,1-dioxide (**3g**) (211 mg, 1 mmol) in CH₃CN (3 ml) was added an CH₃CN solution of piperidine (85 mg, 1 mmol) at –18 °C under N₂. After 20 min a solution of benzoyl chloride (169 mg, 1.2 mmol) in CH₃CN (1.5 ml) was added followed by the addition of a solution of triethylamine (121 mg, 1.2 mmol) in CH₃CN (1.5 ml). The mixture was kept at –18 °C for 1.5 h and gradually warmed to room temperature. The solvent was removed *in vacuo* to give a residue. A crude material was subjected to preparative TLC (benzene) to give pure **4d** (138 mg, 91%). **4a**: Oil; *m/e* 178 (M⁺); IR (neat) 1656, 1200, 901, 673 cm⁻¹; NMR (CDCl₃) δ 3.70 (2H, d, *J*=7.0 Hz), 4.96–5.48 (2H, m), 5.55–6.26 (1H, m), 7.15–8.11 (5H, m). **4b**: Oil; *m/e* 176 (M⁺); IR (neat) 3300, 1660, 1205, 911, 680 cm⁻¹; NMR (CDCl₃)

TABLE 2. PREPARATION OF THIOCARBOXYLIC S-ESTERS (4) AND SULFIDES (5) FROM BID-SR (3) AND ELECTROPHILES

			
BID-SR	Electrophile	Product	Yield/%
3d	PhCOCl	PhCOSCH ₂ CH=CH ₂ ^a (4a)	95 ^a
3e	PhCOCl	PhCOSCH ₂ C≡CH ^a (4b)	91 ^a
3f	PhCOCl	PhCOSCH ₂ C≡N ^a (4c)	89
3g	PhCOCl	PhCOSCH ₂ ^a (4d)	91
3a	CH ₃ COCl	CH ₃ COSCH ₂ Ph ^b (4e)	94 ^b
3a	PhCH ₂ COCl	PhCH ₂ COSCH ₂ Ph ^b (4f)	92 ^b
3a	CH ₃ (CH ₂) ₂ COCl	CH ₃ (CH ₂) ₂ COSCH ₂ Ph ^b (4g)	94 ^b
3a	(CH ₃) ₂ CCOCl	(CH ₃) ₂ CCOSCH ₂ Ph ^b (4h)	33 ^b
3a	CH ₃ COCH=CH ₂	CH ₃ COCH ₂ CH ₂ SCH ₂ Ph ^d (5a)	quant. ^g
3b	CH ₃ COCH=CH ₂	CH ₃ COCH ₂ CH ₂ SCH ₂ CH ₂ Ph ^d (5b)	87
3c	CH ₃ COCH=CH ₂	CH ₃ COCH ₂ CH ₂ SCH ₂ CH=CHPh ^d (5c)	92
3a	CH ₃ -CHCHO	PhCH ₂ SCH ₂ CH ₂ CHO ^{d,e} (5d)	92 ^d
3a	CH ₃ CH=CHCHO	PhCH ₂ SCH ₂ (CH ₂) ₂ CH=CHCHO ^{d,e} (5e)	89 ^d
3a	PhCH=CHCH ₂ Cl	PhCH ₂ SCH ₂ CH=CHPh ^d (5f)	88
3a	(CH ₃) ₂ CHBr	PhCH ₂ SCH ₂ (CH ₃) ₂ ^d (5g)	81 ^d
3a	CH ₃ (CH ₂) ₂ CH ₂ I	PhCH ₂ S(CH ₂) ₄ CH ₃ ^d (5h)	89 ^d
3a	PhCH ₂ Br	PhCH ₂ SCH ₂ Ph ^d (5i)	90 ^d
3a		PhCH=CH(OH)Ph (5j) SCH ₂ Ph (erythro)	quant.

a) Condition: -18°C—room temp, 90 min. b) Room temp, 5 min. c) Room temp, 1.5 h. d) Room temp, 4.5 h. e) Room temp, 5 h. f) Triethylamine used as a base in 4a—h, DBU used in 5a—i, 2.4 equiv. of 1 M NaOH used in 5j. g) They were isolated as 2,4-dinitrophenylhydrazone derivatives.

δ 2.22 (1H, t, $J=2.6$ Hz), 3.83 (2H, d, $J=2.6$ Hz), 7.23—8.17 (5H, m). **4c**: Oil; m/e 177 (M^+); IR (neat) 2985, 1667, 1211, 911 cm^{-1} ; NMR (CDCl_3) δ 3.85 (2H, s), 7.26—8.07 (5H, m). **4d**: Oil; m/e 152 (M^+); IR (neat) 1650, 1195, 902, 673 cm^{-1} ; NMR (CDCl_3) δ 2.45 (3H, s), 7.17—8.07 (5H, m). **4e**: Oil; m/e 166 (M^+); IR (neat) 1680, 1126, 697 cm^{-1} ; NMR (CDCl_3) δ 2.32 (3H, s), 4.10 (2H, s), 7.24 (5H, s). **4f**: Mp 39.5—40.5 °C; m/e 242 (M^+); IR (KBr) 1672, 1014, 697 cm^{-1} ; NMR (CDCl_3) δ 3.71 (2H, s), 3.99 (2H, s), 7.07 (5H, s), 7.14 (5H, s). **4g**: Oil; m/e 194 (M^+); IR (neat) 2959, 1680, 982, 697 cm^{-1} ; NMR (CDCl_3) δ 0.91 (3H, t, $J=7.0$ Hz), 1.66 (2H, t, $J=7.2$, $J=7.0$ Hz), 2.49 (2H, t, $J=7.2$ Hz), 4.03 (2H, s), 7.12 (5H, s). **4h**: Oil; m/e 208 (M^+); IR (neat) 2690, 1672, 949, 697 cm^{-1} ; NMR (CDCl_3) δ 1.24 (9H, s), 4.03 (2H, s), 7.20 (5H, s).

Addition of Thiols to α,β -Unsaturated Carbonyl Compounds (5a—e). Typically, to a solution of 3-(cinnamylthio)-1,2-benzisothiazole 1,1-dioxide (**3c**) (154 mg, 0.5 mmol) in CH_3CN (1 ml) was added a CH_3CN solution of piperidine (43 mg, 0.5 mmol) under N_2 at room temperature. After 30 min a solution of methyl vinyl ketone (38 mg, 0.5 mmol) in CH_3CN (1.5 ml) was added dropwise and then after 3 h a drop of triethylamine was added. The reaction mixture was stirred for additional 1.5 h and evaporated *in vacuo*. Purification with preparative TLC (benzene—ethyl acetate = 10:1 v/v) gave **5a** (101 mg, 92%). **5a**: Oil; m/e 194 (M^+); IR (neat) 1700, 1408, 1353, 693 cm^{-1} ; NMR (CDCl_3) δ 2.09 (3H, s), 2.62 (4H, s), 3.69 (2H, s), 7.26 (5H, s). **5b**: Oil; m/e 208 (M^+); IR (neat) 2920, 1709, 1355, 690 cm^{-1} ; NMR (CDCl_3) δ 2.12 (3H, s), 2.69 (4H, s), 2.80 (4H, s), 7.17 (5H, s). **5c**: Oil; m/e 220 (M^+); IR (neat) 3035, 2933, 1712, 1361, 963 cm^{-1} ; NMR (CDCl_3) δ 2.08 (3H, s), 2.67 (4H, s), 3.25 (2H, d, $J=6.0$ Hz), 6.12 (1H, t, d, $J=6.0$, 15.6 Hz), 6.35 (1H, d, $J=15.6$ Hz), 7.03—7.47 (5H, m).

Compounds (**5d—e**) were not stable to silica gel purification and then characterized as 2,4-dinitrophenylhydrazones, respectively. **5d**: Mp 99.0—99.5 °C (from EtOH); Found: C, 53.24; H, 4.42; N, 15.53%. Calcd for $\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_4\text{S}$: C, 53.32; H, 4.48; N, 15.55%. **5e**: Mp 65.0—65.5 °C (from EtOH); Found: C, 54.40; H, 4.69; N, 14.94%. Calcd for $\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}_4\text{S}$: C, 54.43; H, 4.85; N, 14.96%.

Preparation of the Sulfides (5f—i). Typically, to a suspension of 3-(benzylthio)-1,2-benzisothiazole 1,1-dioxide (**3a**) (142 mg, 0.5 mmol) in CH_3CN (1 ml) was added a solution of piperidine (43 mg, 0.5 mmol) in CH_3CN (1 ml) under N_2 . After stirring for 20 min, a solution of DBU (92 mg, 0.6 mmol) in CH_3CN (1 ml) was added followed by the addition of a solution of benzyl bromide (102 mg, 0.6 mmol) in CH_3CN (1 ml). The reaction mixture was stirred for 5 h and worked up in the usual way. Preparative TLC (hexane—benzene = 5:2 v/v) gave pure **5i** (96 mg, 90%). **5f**: Oil; m/e 240 (M^+); IR (neat) 3049, 1496, 961 cm^{-1} ; NMR (CDCl_3) δ 3.21 (2H, d, $J=6.4$ Hz), 3.62 (2H, s), 6.11 (H, t, d, $J=6.4$, 15.4 Hz), 6.20 (1H, d, $J=15.4$ Hz), 6.92—7.74 (10H, m). **5g**: Oil; m/e 166 (M^+); IR (neat) 2950, 1484, 1443, 1374, 685 cm^{-1} ; NMR (CDCl_3) δ 1.23 (6H, d, $J=6.6$ Hz), 2.68 (1H, q, $J=6.6$ Hz), 3.67 (2H, s), 7.19 (5H, s). **5h**: Oil; m/e 194 (M^+); IR (neat) 2920, 1481, 1443, 685 cm^{-1} ; NMR (CDCl_3) δ 0.63—1.82 (9H, m), 2.37 (2H, t, $J=7.0$ Hz), 3.63 (2H, s), 7.18 (5H, s). **5i**: Oil; m/e 214 (M^+); IR (neat) 3012, 1488, 1445, 685 cm^{-1} ; NMR (CDCl_3) δ 3.53 (4H, s), 7.20 (10H, s). **5j**: Mp 107—108 °C; IR (KBr) 3390, 1595, 1445, 1046 cm^{-1} ; NMR (CDCl_3) δ 2.31 (1H, bs), 3.29 (2H, s), 3.80 (1H, d, $J=6.4$ Hz), 4.85 (1H, d, $J=6.4$ Hz), 6.71—7.61 (15H, m); Found: C, 78.79; H, 6.26%. Calcd for $\text{C}_{21}\text{H}_{20}\text{OS}$: C, 78.71; H, 6.29%.

References

- 1) Y. Suzuki, K. Matsumoto, M. Iwata, S. Seki, and T. Watanabe, Jpn. Kokai Tokkyo Koho, 1978-59029 (Cl. A 01 N 9/14), May 27, 1978; Y. Suzuki, S. Seki, T. Watanabe, and Y. Sekizawa, *ibid.*, 1978-66424 (Cl. A 01 N 9/14), Jun. 13, 1978; Y. Suzuki, S. Seki, T. Watanabe, and Y. Sekizawa, *ibid.*, 1979-35217 (Cl. A 01 N 9/02), Mar. 15, 1979.
- 2) G. L. Bachman, J. W. Baker, and D. P. Roman, *J. Pharm.*, **67**, 1323 (1978).
- 3) S. G. Smith, *J. Am. Chem. Soc.*, **83**, 4285 (1961).
- 4) K. Sato and O. Miyamoto, *Nippon Kagaku Zasshi*, **77**, 1409 (1956).
- 5) J. H. Chapman and L. N. Owen, *J. Chem. Soc.*, **1950**, 579.
- 6) L. S. Godinho and H. J. C. Neves, *Rec. Port. Farm.*, **23**, 592 (1973).
- 7) R. A. Nyquist and W. J. Potts, *Spectrochim. Acta*, **1959**, 514.
- 8) Y. Yokoyama, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.*, **1977**, 25 (9), 2423 (Eng.).
- 9) M. Tanaka, M. Sashio, Y. Shimodori, and M. Murata, *Kogyo Kagaku Zasshi*, **59**, 577 (1956).
- 10) J. R. Catsh, A. H. Cook, A. R. Graham, and I. Heilbron, *J. Chem. Soc.*, **1947**, 1609.
- 11) I. J. Buchi, M. Prost, H. Eichenberger, and R. Lieberherr, *Helv. Chim. Acta*, **35**, 1527 (1952).
- 12) R. Mazingo, D. E. Wolf, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943).