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Reactions of 3*H*-1,2-Benzodithiol-3-one 1-Oxide with Amines and Anilines

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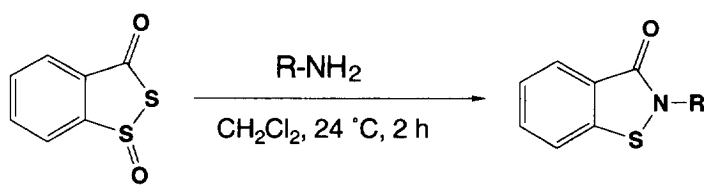
Abstract: Reaction of 3*H*-1,2-benzodithiol-3-one 1-oxide with primary amines or anilines provides reasonable yields (40-70%) of the corresponding 1,2-benzisothiazolin-3(2*H*)-ones. These reactions may have relevance to the biological chemistry of 1,2-dithiolan-3-one 1-oxides and also offer a new method for the preparation of certain 1,2-benzisothiazolin-3(2*H*)-ones.

The antitumor antibiotic leinamycin contains an unusual 1,2-dithiolan-3-one 1-oxide heterocycle that appears to be intimately involved in the thiol-dependent cleavage of DNA by this natural product.[1] We have recently shown that, similar to leinamycin, several simple 1,2-dithiolan-3-one 1-oxide derivatives, including 3*H*-1,2-benzodithiol-3-one 1-oxide (**1**),[2] are thiol-activated DNA-cleaving agents.[3] Our results indicate that simple 1,2-dithiolan-3-one 1-oxides, in concert with thiols, convert molecular oxygen to DNA-cleaving oxygen radicals.[3] Chemical model studies examining the reaction of **1** with thiols have been reported,[4] but the detailed chemical mechanisms of DNA cleavage by this class of compounds remain under investigation.

We describe here reactions of **1** with amines and anilines that may have relevance to the biological chemistry of 1,2-dithiolan-3-one 1-oxides. These reactions lead to formation of a stable bond between nitrogen nucleophiles and **1** under mild conditions, thereby suggesting that covalent adducts might result from reaction of 1,2-dithiolan-3-one 1-oxides with nucleophilic nitrogens in DNA, RNA and proteins.[5] In a separate context, the work described here offers a new method for the preparation of 1,2-benzisothiazolin-3(2*H*)-ones, a class of compounds that is of widespread interest due to their potential as pharmaceuticals.[6] A number of other synthetic routes to 1,2-benzisothiazolin-3(2*H*)-ones have been reported.[6,7]



1 **2**

		Yield
2a	R = -CH_2CH_2Ph	60%
2b	R = cyclohexyl	39%
2c	R = *p*-methoxyphenyl	68%
2d	R = *p*-methylphenyl	64%
2e	R = H	55%

Scheme 1

Treatment of **1** with primary nitrogen nucleophiles or ammonia as shown in Scheme 1 results in a rapid reaction that yields substituted 1,2-benzisothiazolin-3(2*H*)-ones (**2,** Scheme 1).[8] This reaction appears to be rather general; alkylamines, anilines and ammonia react with **1** to afford the corresponding benzisothiazolinone derivatives (**2a-2e**, Scheme 1). Two 1,2-benzisothiazolin-3(2*H*)-ones (**2a** and **2c**) prepared by this method have been characterized by X-ray crystallography and spectroscopic data for compounds **2b-d** agrees with that in the literature.[7] Examination of a series of substituted anilines revealed that this reaction does not extend to derivatives bearing electron withdrawing groups (e.g. *p*-nitroaniline, *p*-aminobenzonitrile); such compounds do not react with **1** at reasonable rates under the conditions described here.

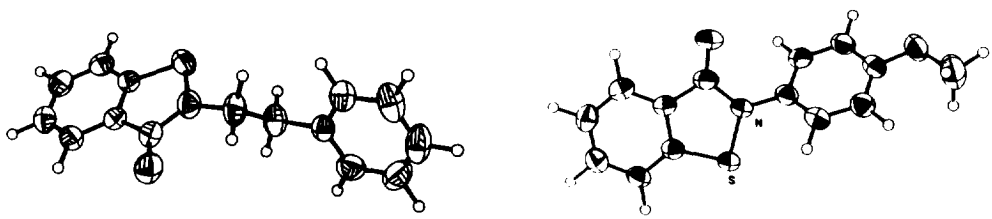
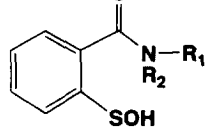


Figure 1. X-Ray Crystal Structures of **2a** (left) and **2c** (right).

Although the mechanism for the formation of 1,2-benzisothiazolin-3(2*H*)-ones in these reactions is not certain, we envision attack of nitrogen on the carbonyl group of **1** leading to expulsion of elemental sulfur[8] and transient formation of 2-(carbamoyl)benzenesulfenic acid **3a**. Similar mechanisms involving extrusion of elemental sulfur have been postulated, for example, in the reactions of 1,2-dithiole-3-thiones with nucleophiles.[9] Sulfenic acids such as **3** are generally unstable species[10] and intramolecular dehydrative cyclization of the amide nitrogen onto the sulfenic acid group can reasonably be expected to yield the observed 1,2-benzisothiazolin-3(2*H*)-one product. This cyclization is analogous to the dehydrative dimerization reaction that is characteristic of sulfenic acids.[10,11]

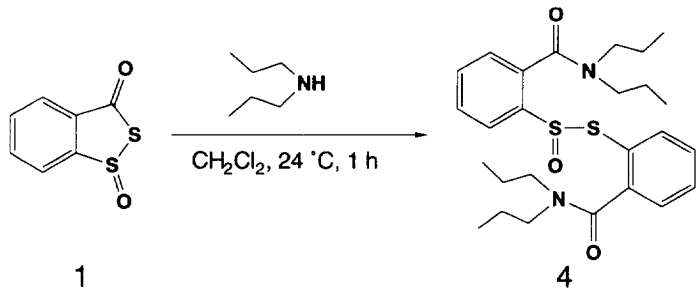


3

3 a, R_1 = H, Ar, or alkyl, R_2 = H

3 b, R_1 and R_2 = *n*-propyl

In accord with the mechanism proposed above, we find that reaction of the secondary amine dipropylamine with **1** yields as a major product thiosulfinate **4** (25%, Scheme 2).[12] We suggest that attack of dipropylamine on the carbonyl group of **1**, similar to the proposed mechanism for monosubstituted amines and anilines, yields the intermediate sulfenic acid **3b**. This sulfenic acid, unable to yield a stable 1,2-benzisothiazolin-3(2*H*)-one product by intramolecular cyclization, presumably undergoes dehydrative dimerization to give the observed thiosulfinate product (**4**).



1 4

Scheme 2

The reactions reported here may be useful for the preparation of certain 1,2-benzisothiazolin-3(2*H*)-ones. Furthermore, this chemistry is of interest as it may relate to the biological properties of 1,2-dithiolan-3-one 1-oxides. Future studies will reveal whether this chemistry serves as a model for the reaction of 1,2-dithiolan-3-one 1-oxides with nitrogen nucleophiles in biological macromolecules.

Acknowledgments: Financial support from NIH (GM51565) and the Petroleum Research Fund (27348-G7) is gratefully acknowledged. We thank the National Science Foundation for support of the NMR facilities at the University of Missouri-Columbia (Grants 9221835 and 8908304) and we are indebted to Dr. Charles Barnes for solving X-ray structures of **2a** and **2b**.

References and Notes

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5. We find that **1** reacts with nucleic acid model, 9-ethyl adenine in dichloromethane. The product(s) of this reaction are, as yet, uncharacterized.
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8. In a typical reaction, **1** (184 mg, 1 mmol) and the appropriate amine or aniline (1.1 eq.) were stirred in dichloromethane (25 mL, distilled from CaH_2) under a nitrogen atmosphere at room temperature until **1** is consumed (1-3 h). In some cases, excess aniline or amine was then removed by extraction with 10% aqueous HCl. The reaction mixture was evaporated to dryness under reduced pressure and the products purified by flash chromatography on silica gel eluted with ethyl acetate-hexane mixtures. In the case of **2e**, a methylene chloride solution containing **1** was saturated with anhydrous ammonia for 1 h and the product isolated as above. **2a**: mp 95-96 °C; ^{13}C NMR ($CDCl_3$, 250 MHz) δ 165.2, 140.2, 137.8, 131.7, 128.9, 128.6, 126.8, 126.6, 125.4, 124.6, 120.3, 45.3, 35.6; HRMS calcd for $C_{15}H_{13}NOS$: 255.0718, found 255.0713 (-1.8 ppm). **2b**: mp 86-88 °C (lit.[7b] 86-88 °C); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 164.8,

140.3, 131.4, 126.5, 125.5, 125.3, 120.3, 53.2, 32.9, 25.6, 25.3; ^{1}H NMR spectral data corresponds to that in the literature.[7f] HRMS calcd for $C_{13}H_{15}NOS$: 233.0874, found 233.0882 (+3.3 ppm). **2c** and **2d**: melting points and spectral data (^{1}H, ^{13}C NMR) are identical to that in the literature.[7e] **2e**: mp 157-158 °C (lit.[7d] 157-158 °C); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 169.1, 144.8, 131.7, 125.9, 125.3, 124.3, 120.7; HRMS calcd for C_7H_5NOS: 151.0092, found 151.0091 (-0.3 ppm). Elemental sulfur is observed (by thin layer chromatography) as a product of these reactions. Sulfur was isolated and characterized from the reaction of **1** with phenethylamine. Anal. calcd for S: S 100%. Found: S 99.7 %.

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12. A mixture of **1** (184 mg, 1 mmol) and dipropylamine (0.15 mL, 1.1 mmol, 1.1 eq.) was stirred in methylene chloride at room temperature under a nitrogen atmosphere for 1 h. The solvent was evaporated under reduced pressure and the resulting mixture separated by flash column chromatography on silica gel eluted with an ethyl acetate-hexane gradient containing 10% triethylamine. Note: Thiosulfinate **4** decomposes slowly on silica gel, but is stable on silica gel that has been neutralized by treatment with triethylamine. Compound **4** is obtained as the major organic-soluble product (light yellow oil, 25%): TLC R_f 0.64 (silica gel 60, Aldrich, 1:1 ethyl acetate:hexane); ^{1}H NMR ($CDCl_3$, 250 MHz, 1:1 mixture of rotamers) δ 7.88-7.77 (m, 2H), 7.41-7.20 (m, 6H), 3.46 (m, 4H), 3.03 (m, 4H), 1.70 (m, 4H), 1.51 (m, 4H), 0.97 (m, 6H), 0.73 (m, 6H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 168.8, 168.7, 138.8, 136.5, 133.7, 133.0, 131.3, 129.5, 129.3, 128.3, 127.8, 126.9, 126.5, 126.5, 50.3, 46.2, 46.0, 21.6, 20.5, 20.4, 11.5, 11.0; IR ($CHCl_3$, cm^{-1}) 2973, 1644, 1426, 1255, 1111, 748. Due to instability of this material, satisfactory elemental analysis and mass spectral data have not been obtained; however, as expected for the thiosulfinate group,[13] treatment of **4** with triphenylphosphine (2.0 eq. PPh_3 in methanol 24° C, 24 h) yielded the corresponding disulfide, 2,2'-dithiodipropylbenzamide (**5**). The disulfide **5** was identical in all respects to material obtained from the reaction of 2,2'-dithiobenzoic acid with thionyl chloride and dipropylamine: TLC R_f 0.58 (1:1 ethyl acetate:hexane); ^{1}H NMR ($CDCl_3$, 500 MHz, 1:1 mixture of rotamers) δ 7.69 (d, 2H, *J*=7.9), 7.33-7.18 (m, 6H), 3.49 (t, 4H, J=7.5), 3.07 (t, 4H, J=7.5), 1.75 (sextet, 4H, J=7.5), 1.50 (sextet, 4H, J=7.4), 1.01 (t, 6H, J=7.4), 0.73 (t, 6H, J=7.4); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 169.1, 136.7, 133.9, 129.6, 127.9, 127.0, 126.6, 50.3, 46.2, 21.6, 20.4, 11.4, 11.0; IR ($CHCl_3$, cm^{-1}) 2964 (m), 1637, 1430, 1257 (w), 1107 (w) 761 (w); HRMS (FAB) calcd for $C_{25}H_{36}N_2O_2S_2Na$ $(M+Na)^+$: 495.2116, found 495.2110 (-1.1 ppm). Oxidation of the thiosulfinate **4** (30% H_2O_2 in acetic acid, 24 °C, 12 h)[14] yielded the corresponding thiosulfonate. This material was identical in all respects to authentic thiosulfonate obtained by oxidation of disulfide **5**.[14] The structure of this thiosulfonate has been confirmed by X-ray crystallography. TLC R_f 0.2 (1:1 ethyl acetate:hexane); ^{1}H NMR ($CDCl_3$, 250 MHz, mixture of rotamers) δ 7.78 (dd, 1H, J_1=7.8, J_2=1), 7.62 (dt, 1H, J_1=7.5, J_2=1), 7.53-7.44 (m, 3H), 7.37-7.31 (m, 3H), 3.4 (br, 4H), 2.97 (t, 4H, J=8), 1.77-1.44 (m, 8H), 1.01-0.90 (m, 6H), 0.76-0.68 (m, 6H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 168.1, 167.7, 143.6, 137.8, 136.6, 133.5, 131.2, 129.6, 129.2, 128.8, 127.8, 127.2, 50.7, 50.2, 46.5, 46.1, 21.7, 21.3, 20.2, 20.0, 11.6, 11.2, 11.1; IR ($CHCl_3$, cm^{-1}) 2967, 1644, 1433, 1334, 1150, 1104, 782.
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Note: Under the reaction conditions reported here, 3*H*-1,2-benzodithiol-3-one (*S*-deoxy-**1**) shows little reactivity with the aniline nucleophiles examined in this study. *S*-deoxy-**1** reacts relatively slowly with phenethylamine and cyclohexylamine, but does not afford the benzisothiazolinone products (**2**). It is reported that treatment of *S*-deoxy-**1** with monosubstituted nitrogen nucleophiles or ammonia in alcoholic solution results in a reaction that yields 2,2'-dithiobis(benzamides) and 1,2-benzisothiazolin-3(2*H*)-one respectively: McKibben, M.; McClellend, E. W. *J. Chem. Soc.* **1923**, *123*, 170-173. McClelland, E. W.; Longwell, J. *J. Chem. Soc.* **1923**, *123*, 3310-3315. For related reactions of 3*H*-1,2-benzodithiole-3-thione with amines see: Pregnolato, M.; Borgna, P.; Terreni, M. *J. Heterocyclic Chem.* **1995**, *32*, 847-850.

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