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

Woongki Kim[‡], Jeffrey Dannaldson[‡] and Kent S. Gates^{‡,†,*}

Departments of Chemistry[‡] and Biochemistry[†], University of Missouri-Columbia, Columbia, MO 65211

Abstract: Reaction of 3H-1,2-benzodithiol-3-one 1-oxide with primary amines or anilines provides reasonable yields (40-70%) of the corresponding 1,2-benzisothiazolin-3(2H)-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(2H)-ones. Copyright © 1996 Elsevier Science Ltd

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 3H-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(2H)-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(2H)-ones have been reported.^{6,7}



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(2H)-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(2H)-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(2H)-ones in these reactions is not certain, we envision attack of nitrogen on the carbonyl group of 1 leading to expulsion of elemental sulfur⁸ 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 species¹⁰ 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(2H)-one product. This cyclization is analogous to the dehydrative dimerization reaction that is characteristic of sulfenic acids.^{10,11}



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(2H)-one product by intramolecular cyclization, presumably undergoes dehydrative dimerization to give the observed thiosulfinate product (4).



The reactions reported here may be useful for the preparation of certain 1.2-benzisothiazolin-3(2H)ones. Furthermore, this chemistry is of interest as it may relate to the biological properties of 1.2-dithiolan-3one 1-oxides. Future studies will reveal whether this chemistry serves as a model for the reaction of 1.2dithiolan-3-one 1-oxides with nitrogen nucleophiles in biological macromolecules.

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- We find that 1 reacts with nucleic acid model, 9-ethyl adenine in dichloromethane. The product(s) of this 5 reaction are, as vet, 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 CaH₂) 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; ¹³C NMR (CDCl₃, 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 C₁₅H₁₃NOS: 255.0718, found 255.0713 (-1.8 ppm). 2b; mp 86-88 °C (lit.7b 86-88 °C); ¹³C NMR (CDCl₃, 250 MHz) & 164.8,

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140.3, 131.4, 126.5, 125.5, 125.3, 120.3, 53.2, 32.9, 25.6, 25.3; ¹H 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 (¹H, ¹³C NMR) are identical to that in the literature.^{7e} **2e**: mp 157-158 °C (lit.^{7d} 157-158 °C); ¹³C NMR (CDCl₃, 250 MHz) δ 169.1, 144.8, 131.7, 125.9, 125.3, 124.3, 120.7; HRMS calcd for C₇H₅NOS: 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); ¹H NMR (CDCl₃, 250 MHz, 1:1 mixture of rotamers) § 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); ¹³C NMR (CDCl₃, 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 (CHCl₃, 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. PPh₃ 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); ¹H NMR (CDCl₃, 500 MHz, 1:1 mixture of rotamers) 8 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); ¹³C NMR (CDCl₃, 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 (CHCl₃, cm⁻¹) 2964 (m), 1637, 1430, 1257 (w), 1107 (w) 761 (w); HRMS (FAB) calcd for C₂₅H₃₆N₂O₂S₂Na (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 R₁ 0.2 (1:1 ethyl acetate:hexane); ¹H NMR (CDCl₃, 250 MHz, mixture of rotamers) § 7.78 (dd, 1H, J₁=7.8, J₂=1), 7.62 (dt, 1H, J₁=7.5, J₂=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); ¹³C NMR (CDCl₃, 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 (CHCl₃, cm⁻¹) 2967, 1644, 1433, 1334, 1150, 1104, 782,
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- Note: Under the reaction conditions reported here, 3H-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-benzisothiazolino-3(2H)-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 3H-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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