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Synthesis of 4*H*-3-aryl-2-cyano-1,4-benzothiazine 1,1-dioxides for antiviral studies

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Abstract: 2-Cyano-substituted 1,4-benzothiazine 1,1-dioxides, required for antiviral studies, were prepared by a reductive cyclodehydration of an *ortho*-nitro sulfone precursor containing a pendant aryl ketone group. The ring-forming reaction also furnishes a non-cyclized benzamide as a major byproduct via an unexpected acyl transfer reaction.

Keywords: 1,4-benzothiazine; acyl transfer; antiviral sulfone; cyclodehydration; iron reduction.

Introduction

The 3,4-dihydrobenzothiazine 1,1-dioxides **1a–b** (Figure 1) have previously been shown by us to have good activity against human beta-herpes viruses, including human cytomegalovirus (HCMV) and human herpes virus 6 (HHV-6) and 7 (HHV-7) [1, 2]. In the case of HHV-6, these compounds act by inhibiting the viral helicase enzyme [3]. To date, however, the benzothiazine analogues **2a,b** have not been described in the literature. Synthesis of compounds **2a,b** as potential antiviral agents is described in this report.

Unsaturated 1,4-benzothiazines have a rich history of biological activity [4] and thus new methods for preparation of this class of compounds often appear in the literature [5–7]. Recently, at least three different ring-forming syntheses of analogs of sulfone derivatives **2** without the cyano substituent at the 2-position have been published [8–10]. While a cyano group could conceivably be added to the 2-position of this core structure to give target compounds **2**, this would seem to be a difficult task and was thus not pursued. Alternatively, compounds **2** could in principle be prepared by dehydrogenation of compounds **1**. Unfortunately, our initial attempts of this one step conversion using oxidizing reagents such as NBS (*N*-bromosuccinimide) were not successful. We thus turned our attention to development of a ring-forming synthesis of compounds **2** that would give the 2-cyano-substituted thiazine directly. Herein, we wish to describe this synthesis and characterization of novel 1,4-benzothiazines **2a,b**.

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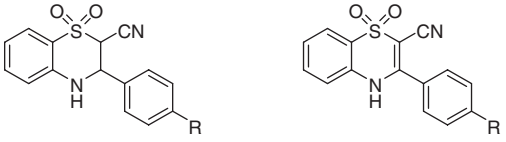
Results and discussion

One of the previously described approaches to the 2-unsubstituted analogs of **2** involves condensation of an *in situ* formed amine group with a pendant aryl ketone (which is linked to an *ortho*-sulfonyl group) to directly provide the unsaturated thiazine ring [8]. We thus envisioned that the cyano-substituted ring system **2** might similarly be prepared starting with an aryl ketone intermediate that has the requisite cyano group already in place. This successful approach is shown in Scheme 1.

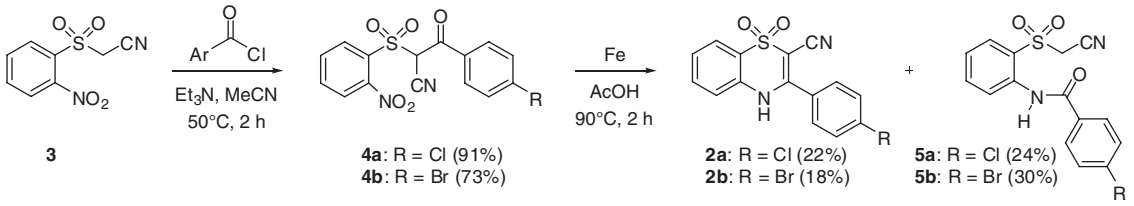
To begin, known 1-(cyanomethyl)sulfonyl-2-nitrobenzene (**3**) [11] was allowed to react with benzoyl chlorides in the presence of triethylamine in acetonitrile to give aryl ketone intermediates **4a,b** in good yields (73%–91%) following purification by column chromatography. Subsequent treatment of these intermediate products with iron powder in acetic acid, conditions similar to that used to prepare compounds **1** [1, 11], gave the desired 2-cyano-substituted compounds **2a,b** via the cyclodehydration reaction. Interestingly, the non-cyclized benzamides **5a,b** were also obtained as major byproducts in this reaction, apparently by a competing acyl group transfer to the *in situ* generated amine group (likely facilitated by the presence of the cyano group which makes the methylsulfonyl moiety a good leaving group for acyl substitution). After purification by column chromatography, target compounds **2a,b**



1a: R = Cl
1b: R = Br

2a: R = Cl
2b: R = Br

Figure 1 Structures of 1,4-benzothiazine derivatives **1** and **2**.



Scheme 1 Synthesis of target compounds **2a,b** and benzamide by products **5a,b**.

were obtained in modest yields of 22% and 18%, respectively. The unexpected benzamides **5a,b** were obtained in slightly higher yields of 24% and 30%. On the basis of TLC analysis of an extract from the iron reduction mixture, no other mobile products were observed after the starting ketone **4** was consumed. Despite the low yield of the target compounds **2a,b**, sufficient quantities for antiviral studies were prepared.

All new compounds prepared in this study were characterized by IR and NMR spectral analysis. Intermediate products **4a,b** appear to exist as mixtures of keto and enol forms based on the presence of both a relatively weak carbonyl absorbance in the IR spectrum at ~1700 cm^{-1} and a broad (and also weak) absorbance at ~3500 cm^{-1} which is assigned to the OH group of the enol tautomer. This suggestion is fully supported by analysis of the ^{1}H NMR and ^{13}C NMR spectra for **4a**. Interestingly, the ^{13}C NMR spectrum of **4b** is consistent with the presence of a single tautomer. For both compounds, a strong signal at ~185 ppm (for a carbonyl carbon) indicates the keto form as the major tautomer. These IR and NMR data are in full agreement with previously reported analysis of an analog of **4a,b** which lacks the nitro and halogen substituents [12].

IR analysis of target compounds **2a,b** and benzamide byproducts **5a,b** was more routine. The conjugated cyano group of **2a,b** shows a strong absorbance at ~2200 cm^{-1}, while the absorbance for the non-conjugated cyano group of benzamides **5a,b** is less intense and shifted to a slightly higher wavenumber (~2250 cm^{-1}), as expected. Each compound gives an NH stretching band in the 3200–3300 cm^{-1} region, while benzamides **5a,b** also show a carbonyl absorbance at ~1665 cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra for products **2a,b** and **5a,b**, as well as the combustion analysis results, are also consistent with the assigned structures.

Conclusions

The 2-cyano-1,4-benzothiazines **2a,b** were prepared by a two-step route that involves a reductive cyclodehydration reaction to give the unsaturated 1,4-thiazine ring directly. The yields are modest (18%–22%) due to the formation of non-cyclized benzamides **5a-b** as unexpected byproducts. Nonetheless, these benzothiazines were prepared in sufficient quantities and are currently undergoing biological screening to determine their antiviral activity.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 at 300 MHz and 75 MHz, respectively, using a Bruker Avance instrument. IR spectra were recorded for neat compounds using ATR. Acetonitrile and triethylamine were distilled from CaH_2. Melting points were recorded in open glass capillaries and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Norcross, GA.

Synthesis of benzoyl intermediates 4a,b

To a solution of nitro sulfone **3** (0.679 g, 3.0 mmol) in dry acetonitrile (4 mL) was added triethylamine (0.607 g, 6.0 mmol) followed by 4-chlorobenzoyl chloride or 4-bromobenzoyl chloride (3.3 mmol) and the dark orange mixture was heated at 50°C for 2 h (**4a**) and for 16 h (**4b**). After cooling, the mixture was treated with HCl (1N, 2 mL) and diluted with excess water. The oily product was extracted with ethyl acetate and the extract was washed with brine and dried over sodium sulfate. Analytically pure product was obtained by silica gel column chromatography eluting with hexanes/EtOAc (1:1) followed by 100% EtOAc.

1-(4-Chlorophenyl)-2-cyano-2-[(2-nitrophenyl)sulfonyl]ethanone (4a) Yield 0.996 g (91%); a yellow-brown solid; mp 142–143.5°C; IR: 3600–3400 (broad and weak), 2197, 1704 (weak) cm^{-1}; ^{1}H NMR: δ 7.40 (d, J = 8 Hz, 2H), 7.57 (d, J = 8 Hz, 2H), 7.72–7.76 (m, 3H), 8.18 (d, J = 8 Hz, 1H); ^{13}C NMR: δ 80.8, 120.4, 123.4, 127.7, 128.8 (minor tautomer), 129.3, 131.1, 131.2 (minor tautomer), 131.5, 132.8, 134.4, 134.4, 136.5, 139.1, 147.3, 181.9. HR-MS. Calcd for $C_{15}H_9ClN_2O_5SNa$ $[M+Na]^+$: m/z 386.9813. Found: m/z 386.9800.

1-(4-Bromophenyl)-2-cyano-2-[(2-nitrophenyl)sulfonyl]ethanone (4b) Yield: 0.898 g (73%); yellow solid, mp 145.5–147°C; IR: 3600–3400 (broad and weak), 2197, 1706 (weak) cm^{-1}; ^{1}H NMR: δ 7.48–7.56 (coalescing doublets, 4H), 7.68–7.78 (m, 3H), 8.16–8.19 (m, 1H) (the tautomer CH/OH was not observed); ^{13}C NMR: δ 80.6, 120.4, 123.1, 123.3, 129.4, 130.6, 131.0, 131.4, 132.7, 136.6, 139.6, 147.3, 182.1 (no signals

observed for a minor tautomer). HR-MS. Calcd for $C_{15}H_9BrN_2O_5SNa$ $[M+Na]^+$: *m/z* 430.9308. Found: *m/z* 430.9290.

Synthesis of benzothiazines 2a,b and benzamides 5a,b

To a solution of **4a** or **4b** (2.70 mmol) in glacial acetic acid (40 mL) was added iron powder (<10 micron) (0.815 g, 14.6 mmol) and the mixture was heated with stirring in an oil bath at 90°C for 2 h. The acetic acid was then removed *in vacuo* and the remaining solid was treated with excess saturated sodium bicarbonate solution and extracted with warm ethyl acetate. The extract was filtered, washed with brine and dried over sodium sulfate. The product mixture **2a/5a** or **2b/5b** was then subjected to silica gel column chromatography eluting with hexanes/EtOAc (5:1) to give benzamide **5a** or **5b** as a white solid. Further elution with hexanes/EtOAc (1:1) gave the target cyclized compound **2a** or **2b** as an off-white solid. Each product was crystallized from the solvent indicated below.

4*H*-3-(4-Chlorophenyl)-2-cyano-1,4-benzothiazine 1,1-dioxide (2a) Yield 22%; mp 264.5–265.5°C (from EtOAc/cyclohexane, white microneedles); IR: 3243, 2204 cm^{-1}; ^1H NMR: δ 7.53–7.64 (m, 3H), 7.74 (d, *J* = 8.7 Hz, 2H), 7.72–7.86 (m, 1H), 7.84 (d, *J* = 8 Hz, 2H), 8.02 (dd, *J* = 8 Hz, 1.2 Hz, 1H), 12.25 (br s, NH); ^{13}C NMR: δ 85.1, 112.6, 119.6, 121.6, 124.1, 126.3, 129.0, 130.0, 131.1, 133.5, 135.0, 137.1, 154.3. Anal. Calcd for $C_{15}H_9ClN_2O_2S$ (316.76): C, 56.88; H, 2.86; N, 8.84. Found: C, 56.75; H, 2.81; N, 8.79.

4-Chloro-*N*-[2-[(cyanomethyl)sulfonyl]phenyl]benzamide (5a) Yield 24%; mp 209–211°C (from MeOH, white fluffy solid); IR: 3325, 2259, 1666 cm^{-1}; ^1H NMR: δ 5.32 (s, 2H), 7.56–7.59 (m, 1H), 7.66 (d, *J* = 8.7 Hz, 2H), 7.88–7.92 (m, 1H), 7.94 (d, *J* = 8.7 Hz, 2H), 8.02 (d, *J* = 8 Hz, 1H), 8.15 (d, *J* = 8 Hz, 1H), 10.41 (s, NH); ^{13}C NMR: δ 44.8, 111.9, 126.1, 126.4, 128.3, 128.9, 129.4, 131.4, 132.6, 136.5, 137.2, 137.2, 164.7. Anal. Calcd for $C_{15}H_{11}ClN_2O_3S$ (334.77): C, 53.82; H, 3.31; N, 8.37. Found: C, 53.74; H, 3.27; N, 8.31.

4*H*-3-(4-Bromophenyl)-2-cyano-1,4-benzothiazine 1,1-dioxide (2b) Yield 18%; mp 270–271°C (from MeOH, white/tan cubic crystals); IR: 3248, 2204 cm^{-1}; ^1H NMR: δ 7.52–7.62 (m, 3H), 7.73 (d, *J* = 8.7 Hz, 2H), 7.72–7.81 (m, 1H), 7.86 (d, *J* = 8.7 Hz, 2H), 8.00 (dd, *J* = 8.1, 1.2 Hz, 1H), 12.24 (br s, NH); ^{13}C NMR: δ 85.6, 113.2, 120.2, 122.1, 124.6, 126.5, 126.8, 130.9, 131.7, 132.5, 134.1, 135.6, 154.9. Anal. Calcd for $C_{15}H_9BrN_2O_2S$ (361.21): C, 49.88; H, 2.51; N, 7.76. Found: C, 49.81; H, 2.43; N, 7.66.

4-Bromo-*N*-[2-[(cyanomethyl)sulfonyl]phenyl]benzamide (5b) Yield 30%; mp 221–222.5 °C (from MeOH, white fluffy solid); IR: 3326, 2258, 1667 cm^{-1}; ^1H NMR: δ 5.32 (s, 2H), 7.57–7.60 (m, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.89–7.92 (m, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 10.41 (s, NH); ^{13}C NMR: δ 44.6, 111.6, 125.9, 125.9, 126.1, 128.1, 129.3, 131.1, 131.6, 132.8, 136.3, 136.9, 164.6. Anal. Calcd for $C_{15}H_{11}BrN_2O_3S$ (379.23): C, 47.51; H, 2.92; N, 7.39. Found: C, 47.33; H, 2.94; N, 7.33.

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