Synthesis of 1,4,2-Benzodithiazine Carboxylates *via* Ring Expansion Reaction of 1,3-Benzodithioles

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In memoriam, Raymond N. Castle

A straight forward synthesis of the 1,4,2-benzodithiazine system bearing an ester functionality as potential inducers of systemic acquired resistance in plants was developed utilizing the ring expansion reaction of 1,3-benzodithioles. The structure of the isomers obtained was established using x-ray diffraction. The reactivity of the products towards activated alkynes and ring contraction reactions in the presence of base is discussed.

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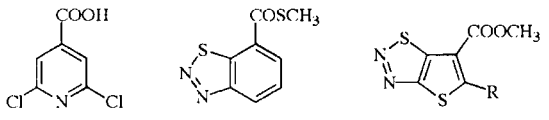
Introduction.

Systemic acquired resistance represents a new concept in plant protection chemistry utilizing the plant's own defense mechanisms. The local infection of a plant may result in developing a resistance to subsequent challenges by a variety of pathogens throughout the whole organism. The expression of PR-proteins plays a major role in this immune response, however, the complete mechanism is not fully understood yet and is the focus point of intensive scientific research [1].

Apart from the infection with a pathogen the stimulation of this effect can also be induced by several heterocyclic compounds usually referred to as plant activators. Molecules like 2,6-dichloroisonicotinic acid **1**, various 1,2,3-benzothiadiazole-7-carboxylic acid derivatives such as **2**, [2] or thiophene fused thiadiazoles **3** [3] are capable of triggering the same biochemical cascade subsequently resulting in an immunization of the plant (Scheme 1). Recently Bion® **2** was introduced as the first commercial product with this novel mode of action.

Scheme 1

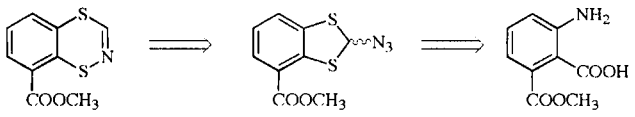


1 **2** **3**

Continuing our previous efforts to find new heterocyclic systems based on the lead structure **2** we became interested in various 6-membered benzo-fused rings changing the nature and number of the heteroatoms. In the present paper we would like to present a synthetic route to the 1,4,2-benzodithiazine system as both a biological target and a versatile intermediate for the preparation of further heteroaromatic compounds. According to the results from biological screening, the ester group adjacent to the anellation site is an important structural feature for activity as an inducer of systemic acquired resistance.

Retrosynthetic analysis of the target compound **I** suggested that **II** is a key intermediate accessible *via* an azide rearrangement (Scheme 2) [4]. The monoester **III** [5] represents a readily available precursor for ester **II** utilizing an aryne methodology. The ester is inert under these conditions enabling a selective introduction of the two sulfur functionalities in a protected form.

Scheme 2



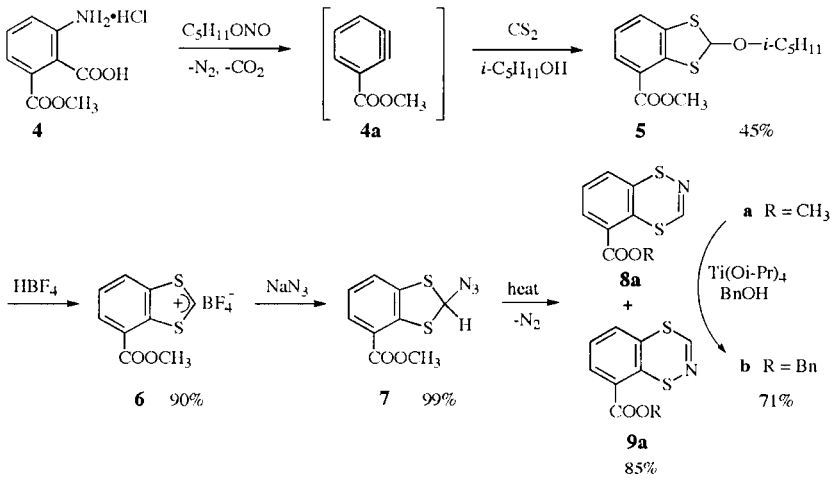
I **II** **III**

Results and Discussion.

Diazotization of hydrochloride **4** with *i*-pentyl nitrite under nonaqueous conditions gave the aryne intermediate **4a** which was quenched by addition of carbondisulfide in the presence of *i*-pentyl alcohol to afford 1,3-benzodithiol **5** in reasonable yield in a one pot sequence (Scheme 3). Treatment of the orthoester **5** with tetrafluoroboric acid lead to the dithiolium salt **6** with the cation stabilized by the tetrafluoroborate counteranion. Introduction of the nitrogen functionality was initiated by conversion to the azide **7** with sodium azide. The subsequent ring expansion to the 1,4,2-benzodithiazine ring system was achieved under thermal conditions. The Schmidt type reaction under nitrogen evolution gave a 1:2 mixture of the two possible isomers **8a** and **9a** in excellent yield. Transesterification was carried out under Lewis acid catalysis in the presence of benzyl alcohol without effect on the ratio of the product mixture to give the esters **8b** and **9b**.

While separation of the methylesters **8/9a** was achieved only by high performance liquid chromatography, the corresponding benzylesters **8/9b** were separated quantitatively on preparative scale *via* flash column chromatography or medium pressure liquid chromatography, respectively.

Scheme 3



Hence, structural assignment of the isomers **8b** and **9b** was finally possible using X-ray diffraction studies of crystalline **9b**. As shown in Figure 1, compound **9b** was unambiguously assigned as 1,4,2-benzodithiazin-8-carboxylic acid ester. The heterocyclic system is clearly not planar but rather in a twisted boat conformation.

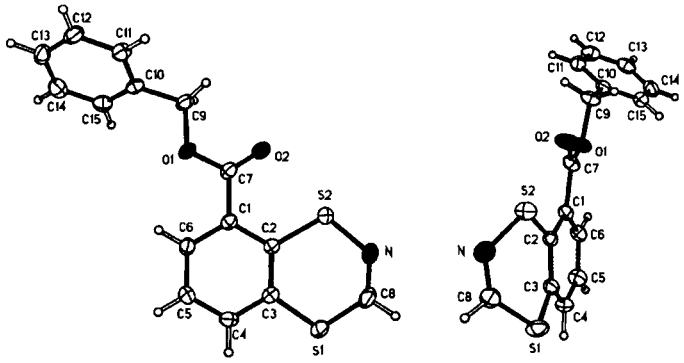
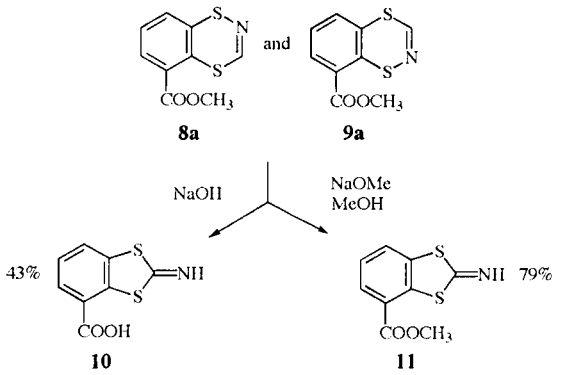


Figure 1

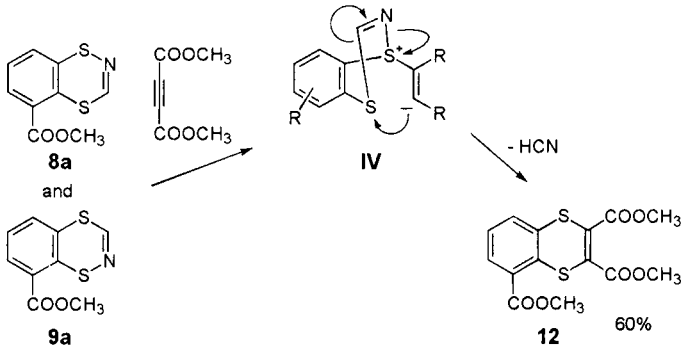
Using **8/9a** as starting material we studied the ring contraction reaction towards the benzodithiol ring system (Scheme 4). Conversion of the esters **8/9a** with sodium methoxide resulted in formation of the expected compound **11**, homogenizing the mixture of isomers to a single product. Under aqueous conditions using sodium hydroxide the ring contraction was accompanied by hydrolysis to the acid **10**. In contrast to indications in the literature we did not observe ring opening reaction to the corresponding dimercaptobenzoic acid ester.[6]

The isomeric mixture of **8/9a** was unified to a single compound in another way by an addition reaction *en route* to 1,4-benzodithiins (Scheme 5): Treatment with dimethyl acetylendicarboxylate under thermal conditions enabled access to the triester **12** *via* elimination of hydrogen cyanide. A mechanism for this type of reaction proceeding *via* an intermediate of type **IV** was proposed in the literature. [7]

Scheme 4



Scheme 5



EXPERIMENTAL

General.

Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification. All solvents were distilled prior to use. Dry diethyl ether was prepared by distillation from sodium/benzophenone, dry methanol by distillation

Table 1

Atomic coordinates and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **9b**. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
S(1)	0.86899(11)	0.05029(6)	0.21855(9)	56(1)
S(2)	0.40847(11)	0.01903(5)	0.39546(8)	48(1)
N(1)	0.4305(4)	0.0000(2)	0.2000(3)	57(1)
O(1)	0.3517(3)	0.2216(1)	0.7885(2)	47(1)
O(2)	0.2879(4)	0.0746(2)	0.6774(2)	62(1)
C(1)	0.5611(4)	0.1774(2)	0.5767(3)	34(1)
C(2)	0.5992(4)	0.1141(2)	0.4505(3)	33(1)
C(3)	0.7850(4)	0.1319(2)	0.3656(3)	38(1)
C(4)	0.9199(4)	0.2131(2)	0.3986(3)	45(1)
C(5)	0.8778(4)	0.2761(2)	0.5201(3)	47(1)
C(6)	0.7009(4)	0.2577(2)	0.6094(3)	40(1)
C(7)	0.3851(4)	0.1516(2)	0.6828(3)	39(1)
C(8)	0.6093(5)	0.0110(3)	0.1346(3)	55(1)
C(9)	0.1934(5)	0.1958(2)	0.9031(3)	47(1)
C(10)	0.1905(4)	0.2788(2)	1.0197(3)	39(1)
C(11)	0.0062(5)	0.3389(2)	1.0236(3)	46(1)
C(12)	0.0005(5)	0.4130(2)	1.1349(3)	53(1)
C(13)	0.1811(6)	0.4278(2)	1.2415(3)	54(1)
C(14)	0.3667(5)	0.3688(2)	1.2363(3)	53(1)
C(15)	0.3714(4)	0.2947(2)	1.1269(3)	45(1)

from magnesium, and dry benzyl alcohol by distillation from calcium oxide. Flash column chromatography was performed on silica gel 60 from E. Merck (40-63 μm) and tlc on Merck precoated silica gel plates. Melting points were determined using a Kofler micro hot stage apparatus and are uncorrected. Elemental analyses were carried out at the Microanalytical Laboratory, University of Vienna. The nmr spectra were recorded on a Bruker AC 200 (200MHz) spectrometer; chemical shifts are reported in ppm using tetramethylsilane as internal standard.

2-(3-Methylbutoxy)-1,3-benzodithiol-4-carboxylic Acid Methyl Ester (**5**).

A refluxing solution of *i*-pentylnitrite (6.60 g, 56.34 mmol), *i*-pentanol (7.40 g, 83.95 mmol), and carbondisulfide (45.00 g, 591.0 mmol) in 1,2-dichloroethane (280 mL) was treated in small portions with 3-aminobenzene-1,2-dicarboxylic acid 1-methylester hydrochloride **4** [5] (10.00 g, 43.17 mmol) over a period of 30 minutes. The mixture was refluxed for additional 2 hours, the solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate. The organic layer was washed with water, saturated sodium bicarbonate solution, and water, dried over sodium sulfate, and concentrated. The crude product was purified by flash column chromatography (silica gel 10:1, petroleum ether:ethyl acetate = 20:1) to give 5.81g (45%) of **5** as yellow oil; ^{1}H nmr (deuteriochloroform): δ 0.83 (d, J = 6 Hz, 6H), 1.41 (q, J = 6 Hz, 2H), 1.60 (m, 1H), 3.43 (t, J = 6 Hz, 2H), 3.93 (s, 3H), 6.71 (s, 1H), 7.15 (t, J = 7 Hz, 1H), 7.52 (dd, J = 7Hz, 1H), 7.83 (dd, J = 7 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 22.2 (q), 24.6 (d), 37.5 (t), 52.2 (q), 62.8 (t), 89.1 (d), 124.3 (s), 124.6 (d), 125.3 (d), 126.9 (d), 138.3 (s), 139.8 (s), 166.0 (s).

Anal. Calcd. for $C_{14}H_{18}O_3S_2$: C, 56.35; H, 6.08. Found: C, 55.95; H, 6.32.

4-Methoxycarbonyl-1,3-benzodithiolium Tetrafluoroborate (**6**).

To an ice cooled solution of dithioorthoester **5** (4.47 g, 14.98 mmol) in acetic anhydride (45 mL) ethereal tetrafluoroboric acid (54% solution, 4.56 mL, 33.21 mmol) was added slowly maintaining the temperature below 5°C. Stirring was continued for 30 minutes before warming to room temperature. The product was precipitated by addition of dry diethyl ether (100 mL) and collected by filtration to give 4.02 g (90%) of **6** as beige crystals, mp 165-170°C (decomposition); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 3.95 (s, 3H), 6.80 (s, 1H), 7.35 (t, J = 7 Hz, 1H), 7.75-7.90 (m, 2H).

2-Azido-1,3-benzodithiol-4-carboxylic Acid Methyl Ester (**7**).

To an ice cooled solution of tetrafluoroborate **6** (4.00 g, 13.42 mmol) in acetonitrile (15 mL) sodium azide (1.74 g, 26.77 mmol) was added in small portions. Stirring was continued for 15 minutes at 0°C and 2 hours at room temperature. The reaction mixture was hydrolyzed, extracted with ethyl acetate, dried over sodium sulfate, and concentrated to afford the crude product which was purified by flash column chromatography (silica gel 10:1, petroleum ether:ethyl acetate = 10:1) to yield 3.35g (98%) of **7** as yellow oil; ^{1}H nmr (deuteriochloroform): δ 3.96 (s, 3H), 6.00 (s, 1H), 7.20 (t, J = 7 Hz, 1H), 7.51 (d, J = 7 Hz, 1H), 7.85 (d, J = 7 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 52.6 (q), 71.3 (d), 124.6 (s), 125.5 (d), 125.6 (d), 127.6 (d), 136.8 (s), 138.5 (s), 166.1 (s).

1,4,2-Benzodithiazine-5-carboxylic Acid Methyl Ester (**8a**) and 1,4,2-Benzodithiazine-8-carboxylic Acid Methyl Ester (**9a**).

A solution of azide **7** (2.11 g, 8.33 mmol) in toluene (40 mL) was refluxed until thin layer chromatography indicated complete consumption of the starting material (usually approximately 2 hours). The solvent was evaporated and the crude material purified by flash column chromatography (silica gel 50:1, petroleum ether:ethyl acetate = 20:1). Product purification gave 1.74 g (85%) of a 1:2 mixture of **8a:9a** as yellow oil. Interpretation of the NMR signals was accomplished by comparison to the corresponding benzyl esters **8/9b**. **8a**: ^{1}H nmr (deuteriochloroform): δ 3.97 (s, 3H), 7.27-7.40 (m, 2H), 7.88 (dd, J = 7 Hz, 1H), 8.22 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 52.5 (q), 127.8 (d), 128.8 (s), 129.4 (d), 130.8 (d), 131.3 (s), 131.9 (s), 155.2 (d), 165.6 (s); **9a**: ^{1}H nmr (deuteriochloroform): δ 3.97 (s, 3H), 7.19-7.27 (m, 2H), 7.88 (dd, J = 7 Hz), 8.22 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 52.5 (q), 124.5 (s), 126.7 (s), 127.8 (d), 130.4 (d), 132.2 (d), 137.6 (s), 152.5 (d), 165.6 (s).

Anal. Calcd. for $C_9H_7NO_2S_2$: C, 47.98; H, 3.13; N, 6.22. Found: C, 48.28; H, 2.97; N, 6.14.

1,4,2-Benzodithiazine-5-carboxylic Acid Phenylmethyl Ester (**8b**) and 1,4,2-Benzodithiazine-8-carboxylic Acid Phenylmethyl Ester (**9b**).

A solution of a mixture of benzodithiazine carboxylic acid methyl esters **8/9a** (0.21 g, 0.93 mmol) obtained according to the above procedure and *i*-propyl orthotitanate (0.1 mL, 0.33 mmol) in dry benzyl alcohol (10 mL) was heated to 100°C for 6 hours. The solvent was removed by *Kugelrohr* distillation (65°C / 0.5 mmHg). A 1:2 mixture of **8b:9b** was isolated as yellow oil in 0.20g (71%) yield. The isomeric mixture of **8b** and **9b** was separable by flash column chromatography (silica gel 50:1, petroleum ether : ethyl acetate = 20:1). **8b**: yellow oil; ^{1}H nmr (deuteriochloroform): δ 5.39 (s, 2H), 7.32-7.52 (m, 7H), 7.92 (dd, J = 6 Hz, 1H), 8.22 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 67.4 (t), 127.7 (d), 128.3 (d), 128.4 (d), 128.5 (d), 128.8 (s), 129.5 (d), 130.8 (d), 131.7 (s), 131.9 (s), 135.1 (s), 155.2 (d), 164.9 (s). **9b**: Yellow crystals, mp 98-100°C; ^{1}H nmr (deuteriochloroform): δ

5.39 (s, 2H), 7.20-7.30 (m, 2H), 7.33-7.50 (m, 5H), 7.92 (dd, J = 6 Hz, 1H), 8.22 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 67.5 (t), 124.7 (s), 126.9 (s), 127.8 (d), 128.4 (d), 128.5 (d), 128.6 (d), 129.6 (d), 132.4 (d), 135.3 (s), 137.9 (s), 152.6 (d), 165.1 (s).

Anal. Calcd. for $C_{15}H_{11}NO_2S_2$: C, 59.79; H, 3.68; N, 4.65. Found: C, 59.48; H, 3.90; N, 4.68.

2-Imino-1,3-benzodithiol-4-carboxylic Acid (**10**).

The isomeric mixture of benzodithiazines **8a/9a** (150 mg, 0.67 mmol) was dissolved in methanol (5 mL) and treated with sodium hydroxide (0.05 g, 1.25 mmol) in water (1 mL). Stirring was continued for 15 minutes at room temperature. The mixture was acidified with 2*N* hydrochloric acid, the precipitated product was collected by filtration, and dried at 50°C *in vacuo* to give 60mg (43%) of **10** as colorless crystals, mp 230°C (decomposition); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.65 (t, J = 8 Hz, 1H), 8.08 (d, J = 8 Hz, 1H), 8.25 (d, J = 8 Hz, 1H); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 126.2 (s), 128.1 (d), 128.5 (d), 129.1 (d), 134.6 (s), 135.2 (s), 166.5 (s), 188.2 (s).

2-Imino-1,3-benzodithiol-4-carboxylic Acid Methyl Ester (**11**).

A solution of benzodithiazines **8a/9a** (140 mg, 0.62 mmol) was dissolved in dry methanol (8 mL) and treated with sodium (40 mg, 1.74 mmol). The mixture was stirred for 10 minutes at room temperature, hydrolyzed, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and the solvent was removed *in vacuo*. Isolation of **11** afforded 110 mg (79%) of beige crystals, mp 113-115°C; ^{1}H nmr (deuteriochloroform): δ 3.96 (s, 3H), 7.25 (t, J = 8 Hz, 1H), 7.45 (d, J = 8 Hz, 1H), 7.92 (d, J = 8 Hz, 1H), 8.90 (bs, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 52.7 (q), 124.3 (s), 125.7 (d), 125.8 (d), 127.9 (d), 137.3 (s), 138.1 (s), 165.6 (s).

Anal. Calcd. for $C_9H_7NO_2S_2$: C, 47.98; H, 3.13; N, 6.22. Found: C, 47.74; H, 2.94; N, 6.02.

1,4-Benzodithiin-2,3,5-tricarboxylic Acid Trimethyl Ester (**12**).

A mixture of esters **8a/9a** (130 mg, 0.58 mmol) and dimethyl acetylendicarboxylate (250 mg, 1.76 mmol) was refluxed in *o*-dichlorobenzene (15 mL) for 15 hours. After removal of the solvent by *Kugelrohr* distillation (70°C/0.02 mmHg) the product was purified by flash column chromatography (silica gel 10:1, petroleum ether:ethyl acetate = 15:1) to yield 120 mg (60%) of **12** as yellow crystals, mp 121-124°C; ^{1}H nmr (deuteriochloroform): δ 3.86 (s, 6H), 3.98 (s, 3H), 7.34 (t, J = 8 Hz, 1H), 7.55 (dd, J = 8 Hz, 1H), 7.88 (dd, J = 8 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 52.6 (q), 53.2 (q), 127.8 (d), 130.2 (d), 130.9 (s), 132.3 (d), 132.8 (s), 133.8 (s), 137.1 (s), 137.2 (s), 162.0 (s), 163.4 (s), 165.7 (s).

Anal. Calcd. for $C_{14}H_{12}O_6S_2$: C, 49.40; H, 3.55. Found: C, 49.12; H, 3.35.

Crystal Structure of **9b**.

A yellow crystal fragment (0.27 x 0.33 x 0.44mm) of **9b** ($C_{15}H_{11}NO_2S_2$, *Fw* = 301.37, monoclinic, space group $P2_1$, a = 6.007(1)Å, b = 13.574(3)Å, c = 8.522(2)Å, β = 94.32(1)°, V = 692.9(3)Å^3, Z = 2, d(calcd) = 1.444g/cm^3, T = 295K) was used for data collection with a PHILIPS PW1100 four-circle diffractometer (MoK_a radiation, λ = 0.71073Å, graphite monochromator, ω-2θ scans, θ = 2.40 - 24°, $0 \le h \le 6$, $0 \le k \le 15$, $-9 \le l \le 9$, 1242 reflections collected, 1136 independent, no correction for absorption, R_{int} = 0.0107). The structure was solved with direct methods (program SHELXS) and refined on F^2 (program SHELXL93) [8] using anisotropic displacement factors for all non-hydrogen atoms. Hydrogen atoms were located from a difference *Fourier* map and were refined in *x,y,z*, and U_{iso} without restraints. Final refinement gave R_1 = 0.0228 and wR_2 = 0.0520 for all 1136 reflections and 182 parameters. R_1 = 0.0209 for the 1087 data with $F_o > 4\sigma(F_o)$. Excursions in final difference Fourier map between -0.12 and 0.15 e Å^{-3}.

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