The preparation of 5-substituted and 4,5-disubstituted 2,1-benzisoxazoles

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Abstract
A series of 5-substituted-2,1-benzisoxazoles has been prepared by the reduction and subsequent cyclization of 5-substituted-2-nitrobenzaldehydes. Reactions of 5-piperidino-2,1-benzisoxazole with nitrous acid and of 5-hydroxy-, 5-N,N-dimethylamino- or 5-pyrrolidino-2,1-benzisoxazole with phenyldiazonium ion led to four 4,5-disubstituted-2,1-benzisoxazoles.

Keywords: Reduction, cyclization, 2,1-benzisoxazoles

Introduction
During investigations of a possible carbon equivalent of the Boulton-Katritzky rearrangement1,2 we required a number of 5-monosubstituted and 4,5-disubstituted-2,1-benzisoxazoles. This paper describes the synthetic route used to obtain these compounds starting from commercially available 5-chloro-2-nitrobenzaldehyde in an adaptation of the versatile method for the synthesis of 2,1-benzisoxazoles (anthranils)3a-b by the reduction of 1-nitrophenones or o-nitroalkylbenzenes containing an oxygen function on the α-carbon of the alkyl substituent.

Results and Discussion
The overall synthetic route from 5-chloro-2-nitrobenzaldehyde 1 is outlined in Scheme 1.
Protection of the aldehyde as its dimethylacetal was followed by displacement of the activated chlorine using a variety of amines (as the neutral bases), alcohols and phenol (sodium alkoxides and phenoxide) and a sulfur nucleophile (thiophenoxide).
Interestingly, compound 3c was obtained as a by-product of the reaction of piperidine, morpholine or pyrrolidine with 2 in amounts depending on the reaction time. For instance when 2 was reacted with morpholine for 8 h the yield of 3c and 3b was 6% and 80% respectively. In contrast when the reaction time was 20 h the yield of 3c increased to 38% and that of 3b fell to 52% (Table).

Table. Yields of 3, 4, and 5

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<th>3 yield (%)</th>
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It seems likely that dimethylamine was generated by an exchange reaction between the amines and DMF followed by reaction of the dimethylamine with 3a, 3b and 3d. Compound 3h, obtained as a by-product (12% yield) of the reaction of sodium butoxide in butanol with 2, presumably arose by exchange between the dimethylacetal 2 and n-butanol. After deprotection of the aldehyde function, reduction of the nitro group and in-situ cyclization was achieved by treatment with stannous chloride dihydrate in conc. HCl at 15 °C over 2 h to give 5a-g in yields of 52-90%. Novel compounds 5a-g were characterized by elemental analysis, mass spectrometry and $^1$H/$^{13}$C NMR. In each case the cyclization was supported by $^1$H NMR spectra which showed a new set of singlets at 8.79-9.01 ppm assigned to H-3 of the isoxazole ring. The $^{13}$C NMR spectra of 5a-g also showed signals between 150.0 ppm and 153.7 ppm corresponding to C-3 of the isoxazole ring. We noted a linear correlation ($r^2 = 0.955$) between the chemical shifts of the
$^{13}$C and $^1$H resonance signals of C-3 and H-3 of the isoxazole ring. Thus the 5-thiophenyl substituent affords the greatest downfield shift of both C-3 and H-3 and conversely the pyrrolidino group leads to the highest degree of shielding.

Attempted nitrosation of 5a occurred as expected, but was accompanied by hydrolysis of the piperidino group with formation of 6 in 98% isolated yield, a compound that was previously synthesized by nitrosation of 5-hydroxy-2,1-benzisoxazole (7, Scheme 2).

Compound 7 coupled with phenyldiazonium cation to form 8 in 91% isolated yield (Scheme 2). Structure 8 was supported by $^1$H/$^{13}$C NMR which revealed a carbonyl carbon at 180.4 ppm consistent with the keto-imino tautomer. Successful azo coupling to form 9 and 10 was also effected with 5c and 5d in 13% and 51% isolated yields respectively (Scheme 2). It should be noted that introduction of the phenylazo group at position 4 of 5c and 5d caused C-3 and H-3 of the isoxazole ring to move even further downfield (for 9: 155.9 and 9.82 ppm; for 10: 155.6 and 9.89 ppm). However azo compounds 9 and 10 were unstable in CDCl$_3$ and considerable decomposition was detected overnight at RT.

![Scheme 2](image)

All attempts to achieve thermal or base-promoted rearrangement of 6, 8, 9 or 10 with opening of the isoxazole ring and simultaneous closure of a new five membered ring (e.g. 8 $\rightarrow$ 11) resulted in either no reaction or substantial decomposition. It is clear that it is not easy to deprotonate the isoxazole ring and even if H-3 is removed under vigorous conditions the anion formed is not stable enough to allow the anticipated rearrangement. Further efforts to effect the rearrangement are under investigation.

In conclusion, a facile route to 5-substituted-2,1-benzisoxazoles is described and azo coupling of the 5-hydroxy, 5-$N,N$-dimethylamino- and 5-pyrrolidino derivatives is reported.
Experimental Section

General Procedures. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl and N,N-dimethylformamide (DMF) was dried over molecular sieve (4A) prior to use. All other solvents and reagents were obtained from commercial suppliers and were used without further purification. Melting points are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded (300 and 75 MHz, respectively) in CDCl$_3$ (with TMS for $^1$H and chloroform-d for $^{13}$C as the internal reference). Elemental and mass spectrometry analyses were performed by Analytical Laboratories, Dept. of Chem., University of Florida. Column chromatography was carried out using 200-425 mesh silica gel.

5-Chloro-2-nitrobenzaldehyde dimethylacetal (2). A solution of 5-chloro-2-nitrobenzaldehyde (Aldrich, 80% purity, 1.00 g, 4.31 mmol), methyl orthoformate (1.01 g, 9.5 mmol) and dry methanol (0.304 g, 9.5 mmol) in dry THF (30 ml) was heated under reflux for 2 h under argon in the presence of a catalytic amount (0.04 g, 0.21 mmol) of $p$-toluene sulfonic acid. After cooling to ambient the solvent was evaporated and the residue purified by column chromatography on silica gel using hexane/ethyl acetate (5/1, v/v) as eluent to yield (0.89 g, 89%) of 2 as a yellow oil, $^1$H NMR, $\delta$ 3.42 (s, 6H), 5.93 (s, 1H), 7.45 (dd, $J = 8.5$, 2.3 Hz, 1H) 7.79 (d, $J = 2.3$ Hz, 1H), 7.81 (d, $J = 8.5$ Hz, 1H); $^{13}$C NMR, $\delta$ 54.7 ($\text{C}_2\text{H}_3$), 99.2 ($\text{C}_7\text{H(OCH}_3)_2$), 125.8 ($\text{C}_6\text{H}$), 128.4 ($\text{C}_6\text{H}$), 129.3 ($\text{C}_6\text{H}$), 134.8 ($\text{C}_7\text{q}$), 139.1 ($\text{C}_7\text{q}$), 146.9 ($\text{C}_7\text{q}$).

1-[3-(Dimethoxymethyl)-4-nitrophenyl]piperidine (3a). Following a literature procedure a mixture of 2 (0.8 g, 3.45 mmol) and excess anhydrous piperidine (1.57 g, 18.42 mmol) in DMF (5 ml) was stirred under argon at 80 $^\circ$C for 8 h. After removal of the solvent, the liquid residue was poured into 0.5 M aq. NaOH (50 ml), extracted into dichloromethane (3 x 50 ml) and the combined extracts dried over anhydrous MgSO$_4$. Evaporation of the solvent left a brown liquid that was purified by column chromatography on silica gel (hexanes/ethyl acetate, 3/1, v/v as eluent) to give (0.85 g, 3.03 mmol, 88%) of 3a as a yellow oil which on standing at 0 $^\circ$C gave a yellow solid, mp 52-54 $^\circ$C. $^1$H NMR $\delta$ 1.67-1.71 (m, 6H), 3.39-3.50 (m, 10H), 6.08 (s, 1H), 6.75 (dd, $J = 9.2$, 2.9 Hz, 1H), 7.17 (d, $J = 2.9$ Hz, 1H), 8.03 (d, $J = 9.2$ Hz, 1H); $^{13}$C NMR, 24.1 ($\text{C}_2\text{H}_2$), 25.2 ($\text{C}_2\text{H}_2$), 48.2 ($\text{C}_7\text{H}_2$), 55.4 ($\text{C}_7\text{OCH}_3$), 101.0 [$\text{C}_7\text{H(OCH}_3)_2$], 111.1 (CH), 112.1 (CH), 128.2 (CH), 136.0 ($\text{C}_7\text{q}$), 136.7 ($\text{C}_7\text{q}$), 154.0 ($\text{C}_7\text{q}$). Anal. Calcd for C$_{14}$H$_{20}$N$_2$O$_4$: C, 59.98; H, 7.19; N, 9.99. Found: C, 60.28; H, 7.49; N, 10.21.

A later fraction was also separated as a yellow oil that crystallized to a yellow solid, mp 69-71$^\circ$C and proved to be 5-($N,N$-dimethylamino)-2-nitrobenzaldehyde dimethylacetal (3c) (0.05 g, 0.21 mmol, 6%). $^1$H NMR $\delta$ 3.11 (s, 6H), 3.48 (s, 6H), 6.10 (s, 1H), 6.57 (dd, $J = 9.3$, 2.9 Hz, 1H), 7.00 (d, $J = 2.9$ Hz, 1H), 8.06 (d, $J = 9.3$ Hz, 1H); $^{13}$C NMR $\delta$ 40.1 ($\text{C}_7\text{NCH}_3$), 55.5 ($\text{C}_7\text{OCH}_3$), 101.1 [$\text{C}_7\text{H(OCH}_3)_2$], 109.0 (CH), 110.0 (CH), 128.2 (CH), 136.1 ($\text{C}_7\text{q}$), 136.2 ($\text{C}_7\text{q}$), 153.4 ($\text{C}_7\text{q}$). Anal. Calcd for C$_{11}$H$_{16}$N$_2$O$_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.16, H, 7.02, N, 11.64.

Similar reaction conditions were used for the preparation of 3b and 3d with reaction times of 8 h and 9 h respectively.
aqueous solution was extracted with ether (3 ml). After cooling the reaction mixture was poured into water (60 ml) and the resulting solution was filtered. The combined ether extracts were dried (the second fraction) and isolated as a yellow oil (1.35 g, 5.82 mmol) in DMF (20 ml) was heated at 80 °C under nitrogen for 9 h. After evaporation of the solvent the residue was chromatographed on silica gel using hexane/dichloromethane (100/1-30/1, v/v) as eluent to give 3e (0.46 g, 43%) as a pale yellow oil (the third fraction) and 2-(dimethoxymethyl)-4-methoxy-1-nitrobenzene (3f) (0.11 g, 12%) as brown oil (the third fraction). \( ^1H \) NMR for 3e \( \delta 0.98 \) (t, \( J = 7.4 \) Hz, 3H), 1.44-1.56 (m, 2H), 1.75-1.84 (m, 2H), 3.44 (s, 6H), 4.06 (t, \( J = 6.4 \) Hz, 2H), 6.01 (s, 1H), 6.89 (dd, \( J = 9.0 \), 2.9 Hz, 1H), 7.28 (d, \( J = 2.9 \) Hz, 1H), 7.98 (d, \( J = 9.0 \) Hz, 1H); \( ^{13}C \) NMR \( \delta 13.8 \) (CH3), 19.1 (CH2), 31.0 (CH2), 55.1 (2/CH3), 68.5 (OCH3), 100.2 (CH2OCH3), 113.2 (CH), 114.3 (CH), 127.3 (CH), 136.0 (Cq), 141.1 (Cq), 162.8 (Cq). Anal. Calcd for C13H19NO2: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.94; H 7.49; N, 5.49. \( ^1H \) NMR for 3h \( \delta 3.44 \) (s, 6H), 3.91 (s, 3H), 6.01 (s, 1H), 6.91 (dd, \( J = 9.0 \), 2.6 Hz, 1H), 7.30 (d, \( J = 2.6 \) Hz, 1H), 7.98 (d, \( J = 9.0 \) Hz, 1H); \( ^{13}C \) NMR \( \delta 55.1 \) (2/CH3), 55.9 (OCH3), 100.1 (CH2OCH3), 112.8 (CH), 114.0 (CH), 127.3 (CH), 136.0 (Cq), 141.4 (Cq), 163.0 (Cq). Anal. Calcd for C10H13NO3: C, 52.86; H, 5.77; N, 6.16. Found: C, 53.22; H, 6.00; N, 6.36.

2-Dimethoxymethyl-4-phenoxynitrobenzene (3f). A solution of sodium phenoxide (0.68 g, 5.82 mmol) and 2 (1.35 g, 5.82 mmol) in DMF (20 ml) was heated at 80 °C with stirring for 13 h. After evaporation of the solvent the residue was chromatographed on silica gel (hexane/dichloromethane, 100/1-30/1, v/v as eluent) to give 3f from the second fraction as a yellow oil (1.14 g, 3.94 mmol, 68%). \( ^1H \) NMR \( \delta 3.41 \) (s, 6H), 5.97 (s, 1H), 6.93 (dd, \( J = 8.8 \), 2.9 Hz, 1H), 7.07 (d, \( J = 7.8 \) Hz, 2H), 7.24 (t, \( J = 7.4 \) Hz, 1H), 7.38-7.45 (m, 3H), 7.93 (d, \( J = 8.8 \) Hz, 1H); \( ^{13}C \) NMR \( \delta 55.0 \) (2/CH3), 100.0 (CH2OCH3), 116.6 (CH), 116.8 (CH), 120.2 (2/CH), 125.1 (CH), 127.2 (CH), 130.2 (2/CH), 136.1 (Cq), 142.8 (Cq), 154.8 (Cq), 161.6 (Cq). Anal. Calcd for C15H15NO2: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.23; H, 5.14; N, 5.16.

2-Dimethoxymethyl-4-phenylsulfanylnitrobenzene (3g). A solution of sodium thiophenoxide (0.52 g, 3.97 mmol) and 2 (0.92 g, 3.97 mmol) in DMF (50 ml) was heated at 80 °C under nitrogen for 11 h. After cooling the reaction mixture was poured into water (60 ml) and the aqueous solution was extracted with ether (3 x 60 ml). The combined ether extracts were dried.
(MgSO₄), filtered and after evaporation of the solvent the residue was chromatographed on silica gel (hexane/dichloromethane as eluent starting at 150/1, v/v but gradually increasing the polarity) to give (3.0 g, 1.03 mmol, 85%) from the second fraction as yellow prisms, mp 56-57 °C. ¹H NMR δ 3.38 (s, 6H), 5.91 (s, 1H), 7.07 (dd, J = 8.5, 1.4 Hz, 1H), 7.42-7.46 (m, 3H), 7.47-7.55 (m, 2H), 7.57 (d, J = 1.4 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H); ¹³C NMR δ 54.9 (2/OCH₃), 99.9 [CH(OCH₃)₂], 125.4 (CH), 126.1 (CH), 126.9 (CH), 129.4 (CH), 129.9 (2/CH), 130.9 (C₀), 133.7 (C₀), 134.4 (2/CH), 145.8 (C₀), 146.0 (C₀). Anal. Calcd for C₁₅H₁₅NO₄S: C, 58.99; H, 4.95; N, 4.59. Found: C, 58.61; H, 5.03; N, 4.85.

**General procedure for the preparation of (4a-g)**

The hydrolysis procedure for the preparation of 4a-g was essentially the same throughout and is exemplified by the preparation of 2-nitro-5-piperidinobenzaldehyde 4a. A solution of 3a (2.65 g, 9.45 mmol) and conc. HCl (1.64 ml) in isopropanol (23 ml) was heated under reflux for 1h. After evaporation of the solvent, water (50 ml) was added to the residue and the resultant solution was extracted with ethyl acetate (3 × 50 ml). The combined extracts were dried (MgSO₄), filtered and the solvent evaporated to give a residue that was chromatographed on silica gel using hexane/ethyl acetate, 3/1, v/v, as eluent to give 4a (2.1 g, 8.98 mmol, 95%) as yellow needles, mp 99-100 °C. ¹H NMR δ 1.62-1.71 (m, 6H), 3.49-3.52 (m, 4H), 6.91 (dd, J = 9.3, 2.9 Hz, 1H), 7.09 (d, J = 2.9 Hz, 1H), 8.09 (d, J = 9.3 Hz, 1H), 10.52 (s, 1H); ¹³C NMR δ 24.1 (CH₂), 25.2 (2/CH₂), 48.3 (2/NCH₂), 112.1 (CH), 114.7 (CH), 127.8 (CH), 135.6 (C₀), 137.0 (C₀), 154.0 (C₀), 190.3 (CHO). Anal. Calcd for C₁₂H₁₄N₂O₅: C, 61.53; H, 6.02; N, 11.92. Found: C, 61.42; H, 6.10; N, 11.85.

**2-Nitro-5-morpholinobenzaldehyde (4b).** Yield 96%, yellow needles, mp 164-166 °C. ¹H NMR δ 3.40-3.50 (m, 4H), 3.84-3.92 (m, 4H), 6.97 (dd, J = 9.3, 2.6 Hz, 1H), 7.15 (d, J = 2.6 Hz, 1H), 8.13 (d, J = 9.3 Hz, 1H), 10.52 (s, 1H); ¹³C NMR δ 46.8 (2/NCH₂), 66.2 (2/OCH₂), 112.4 (CH), 115.2 (CH), 127.5 (CH), 134.6 (C₀), 138.7 (C₀), 154.2 (C₀), 189.7 (CHO). Anal. Calcd for C₁₁H₁₂N₂O₄: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.65; H, 5.14; N, 11.62.

**2-Nitro-5-dimethylaminobenzaldehyde (4c).** Yield 72%, yellow needles, mp 125-127 °C. ¹H NMR δ 3.16 (s, 6H), 6.72 (dd, J = 9.4, 2.9 Hz, 1H), 6.86 (d, J = 2.9 Hz, 1H), 8.07 (d, J = 9.4 Hz, 1H), 10.49 (s, 1H); ¹³C NMR δ 40.2 (2/NCH₂), 110.0 (CH), 112.8 (CH), 127.5 (CH), 135.1 (C₀), 136.3 (C₀), 153.4 (C₀), 190.3 (CHO). Anal. Calcd for C₀H₁₀N₂O₃: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.58; H, 5.08; N, 14.29.

**2-Nitro-5-(1-pyrrolidinyl)benzaldehyde (4d).** Yield 94%, orange needles, mp 127-129 °C. ¹H NMR δ 2.02-2.20 (m, 4H), 3.30-3.50 (m, 4H), 6.59 (dd, J = 9.1, 2.5 Hz, 1H), 6.75 (d, J = 2.5 Hz, 1H), 8.09 (d, J = 9.1 Hz, 1H), 10.51 (s, 1H). ¹³C NMR δ 25.4 (2/CH₂), 48.1 (2/NCH₂), 110.5 (CH), 113.0 (CH), 127.8 (CH), 135.6 (C₀), 136.0 (C₀), 151.2 (C₀), 190.5 (CHO). Anal. Calcd for C₁₁H₁₂N₂O₃: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.12; H, 5.56; N, 12.66.

**2-Nitro-5-n-butoxybenzaldehyde (4e).** Yield 100%, pale yellow prisms, mp 35-37 °C. ¹H NMR δ 0.99 (t, J = 7.5 Hz, 3H), 1.45-1.57 (m, 2H), 1.78-1.87 (m, 2H), 4.11 (t, J = 6.5 Hz, 2H), 7.14 (dd, J = 9.0, 2.9 Hz, 1H), 7.31 (d, J = 2.9 Hz, 1H), 8.15 (d, J = 9.0 Hz, 1H), 10.49 (s, 1H); ¹³C NMR δ 13.7 (CH₃), 19.0 (CH₂), 30.8 (CH₂), 69.0 (OCH₂), 113.7 (CH), 118.9 (CH), 127.2 (CH),
134.4 (C₉), 142.0 (C₈), 163.7 (C₆), 188.6 (CHO). Anal. Caled for C₁₁H₁₃NO₄: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.20; H, 6.01; N, 6.49.

2-Nitro-5-phenoxylbenzaldehyde (4f). Yield 92%, brown oil. ¹H NMR δ 7.09 (d, J = 7.9 Hz, 2H), 7.20 (dd, J = 8.9, 2.7 Hz, 1H), 7.29 (t, J = 7.9 Hz, 1H), 7.35 (d, J = 2.7 Hz, 1H), 7.46 (t, J = 7.9 Hz, 2H), 8.16 (d, J = 8.9 Hz, 1H), 10.43 (s, 1H); ¹³C NMR δ 116.6 (CH), 120.5 (3/CH), 125.9 (CH), 127.3 (CH), 130.5 (2/CH), 134.3 (C₈), 143.1 (C₇), 154.0 (C₆), 162.9 (C₅), 188.0 (CHO). HRMS (EI) m/z Caled for C₁₃H₉NO₄: 243.0532. Found: 243.0533.

2-Nitro-5-(phenylsulfanyl)benzaldehyde (4g). Yield 81%, yellow prisms, mp 52-54 °C. ¹H NMR δ 7.29 (dd, J = 8.8, 2.3 Hz, 1H), 7.46-7.59 (m, 6H), 7.98 (d, J = 8.8 Hz, 1H), 10.39 (s, 1H); ¹³C NMR δ 125.2 (CH), 126.2 (CH), 129.3 (C₇), 129.7 (CH), 130.1 (CH), 130.2 (2/CH), 132.2 (C₆), 134.9 (2/CH), 145.8 (C₈), 149.2 (C₅), 188.1 (CHO). Anal. Caled for C₁₃H₉NO₃S: C, 60.22; H, 3.50; N, 5.40. Found: C, 60.05; H, 3.35; N, 5.25.

General procedure for the preparation of (5a-g)⁶

The cyclisation procedure for the preparation of 5a-g was essentially the same throughout and is exemplified by the preparation of 5-piperidino-2,1-benzisoxazole (5a). A sample of 4a (3.00 g, 12.81 mmol) was added to a cooled (15°C) rapidly stirred solution of stannous chloride dihydrate (11.63 g, 51.54 mmol) in conc. HCl (31 ml). After 2 h the reaction mixture was neutralized with a saturated solution of aqueous sodium bicarbonate and the mixture was extracted with ether (3 × 60 ml). The combined extracts were dried (MgSO₄), filtered and after evaporation of the solvent the residue was chromatographed on silica gel using hexane/ethyl acetate (3/1, v/v) as eluent to give grey crystals of 5a (1.93 g, 9.54 mmol, 74%), mp 49-51 °C. ¹H NMR δ 1.57-1.63 (m, 2H), 1.70-1.77 (m, 4H), 3.06-3.10 (m, 4H), 6.60 (s, 1H), 7.21 (dd, J = 9.8, 1.8 Hz, 1H), 7.50 (d, J = 9.8 Hz, 1H), 8.86 (s, 1H); ¹³C NMR δ 24.1 (CH₂), 25.8 (2/CH₂), 51.2 (2/NCH₂), 98.0 (CH), 115.4 (CH), 118.9 (C₇), 129.6 (CH), 148.7 (C₈), 151.7 (CH), 154.2 (C₅). Anal. Caled for C₁₂H₁₄N₂O: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.64; H, 7.11; N, 13.51.

5-Morpholino-2,1-benzisoxazole (5b). Yield 77%, green prisms, mp 122-124 °C. ¹H NMR δ 3.08-3.16 (m, 4H), 3.84-3.92 (m, 4H), 6.62 (d, J = 1.8 Hz, 1H), 7.20 (dd, J = 9.8, 1.8 Hz, 1H), 7.53 (d, J = 9.8 Hz, 1H), 8.91 (s, 1H); ¹³C NMR δ 50.1 (2/NCH₂), 66.7 (2/OCH₂), 98.3 (CH), 115.9 (CH), 118.6 (C₇), 128.2 (CH), 147.7 (C₈), 152.2 (CH), 154.3 (C₅). Anal. Caled for C₇H₁₀N₂O₂: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.63; H, 6.14; N, 13.43.

5-N,N-Dimethylamino-2,1-benzisoxazole (5c). Yield 74%, green prisms, mp 76-78 °C. ¹H NMR δ 2.94 (s, 6H), 6.38 (s, 1H), 7.23 (d, J = 9.0 Hz, 1H), 7.52 (d, J = 9.0 Hz, 1H), 8.84 (s, 1H); ¹³C NMR δ 41.2 (2/NCH₂), 93.7 (CH), 115.5 (CH), 119.3 (C₇), 126.5 (CH), 147.0 (C₆), 150.9 (CH), 153.7 (C₅). Anal. Caled for C₉H₁₀N₂O: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.70; H, 6.38; N, 17.10.

5-(1-Pyrrolidinyl)-2,1-benzisoxazole (5d). Yield 60%, dark green prisms, mp 110-112 °C. ¹H NMR δ 2.01-2.05 (m, 4H), 3.32-3.36 (m, 4H), 6.13 (s, 1H), 7.11 (dd, J = 9.6, 1.8 Hz, 1H), 7.52 (d, J = 9.6 Hz, 1H), 8.79 (s, 1H); ¹³C NMR δ 25.4 (2/CH₂), 48.1 (2/NCH₂), 89.7 (CH), 115.6 (CH), 119.7 (C₇), 125.5 (CH), 143.7 (C₈), 150.0 (CH), 153.6 (C₅). Anal. Caled for C₁₁H₁₂N₂O: C, 70.19; H, 6.43; N, 14.88. Found: C, 69.98; H, 6.57; N, 14.81.
5-n-Butoxy-2,1-benzisoxazole (5e). Yield 58%, yellow oil. \(^1\)H NMR \(\delta\) 0.99 (t, \(J = 7.3\) Hz, 3H), 1.43-1.57 (m, 2H), 1.71-1.85 (m, 2H), 3.94 (t, \(J = 6.3\) Hz, 2H), 6.60 (s, 1H), 7.03 (dd, \(J = 9.5, 2.1\) Hz, 1H), 7.52 (d, \(J = 9.5\) Hz, 1H), 8.90 (s, 1H); \(^13\)C NMR \(\delta\) 13.8 (CH\(_3\)), 19.2 (CH\(_2\)), 31.0 (CH\(_2\)), 67.7 (OCH\(_2\)), 93.1 (CH), 116.3 (CH), 118.3 (C\(_q\)), 128.5 (CH), 152.1 (CH), 154.3 (C\(_q\)), 155.5 (C\(_q\)). Anal. Calcd for C\(_{11}\)H\(_{13}\)NO\(_2\): C, 69.09; H, 6.85; N, 7.32. Found: C, 69.14; H, 7.03; N, 7.52.

5-Phenoxy-2,1-benzisoxazole (5f). Yield 52%, colorless prisms mp 50.0-52.0 °C. \(^1\)H NMR \(\delta\) 6.81 (s, 1H), 7.07 (d, \(J = 7.9\) Hz, 2H), 7.15-7.20 (m, 2H), 7.39 (t, \(J = 7.9\) Hz, 2H), 7.64 (d, \(J = 9.6\) Hz, 1H), 8.95 (s, 1H); \(^13\)C NMR \(\delta\) 102.0 (CH), 117.1 (CH), 118.0 (C\(_q\)), 119.5 (2/CH), 124.2 (CH), 127.9 (CH), 130.0 (2/CH), 153.4 (CH), 154.1 (C\(_q\)), 154.4 (C\(_q\)), 155.9 (C\(_q\)). Anal. Calcd for C\(_{13}\)H\(_9\)NO\(_2\): C, 73.93; H, 4.30; N, 6.63. Found: C, 74.08; H, 4.25; N, 6.89.

5-(Phenylsulfanyl)-2,1-benzisoxazole (5g). Yield 90%, yellow prisms, mp 74-76 °C. \(^1\)H NMR \(\delta\) 7.19 (dd, \(J = 9.5, 1.5\) Hz, 1H), 7.30-7.43 (m, 5H), 7.45 (s, 1H), 7.56 (d, \(J = 9.5\) Hz, 1H), 9.01 (s, 1H); \(^13\)C NMR \(\delta\) 115.9 (CH), 118.6 (C\(_q\)), 119.6 (CH), 127.8 (CH), 129.4 (2/CH), 131.7 (2/CH), 132.6 (C\(_q\)), 133.8 (CH), 134.0 (C\(_q\)), 153.7 (CH), 155.1 (C\(_q\)). Anal. Calcd for C\(_{13}\)H\(_9\)NOS: C, 68.70; H, 3.99; N, 6.16. Found: C, 68.38; H, 3.86; N, 6.06.

2,1-Benzisoxazole-4,5-dione 4-oxime (6). \(^1\)H-Piperidino-2,1-benzisoxazole 5a (0.30 g, 1.48 mmol) was dissolved in concentrated hydrochloric acid (4.0 ml) and cooled in an ice bath until the temperature fell below 5 °C. A solution of sodium nitrite (0.11 g, 1.55 mmol) in water (2.0 ml) was added dropwise to the cooled (0-5 °C) rapidly stirred reaction mixture. After all the nitrite solution was added the reaction mixture was stirred for 50 min at 0-5 °C. Water (60 ml) was added and the mixture was extracted with methylene chloride (3×60 ml). One hour after the extraction the first crop of 6 precipitated in the aqueous phase, which was filtered off and dried (0.10 g, 0.61 mmol, 41%). The organic phase was dried (MgSO\(_4\)), and the solvent was removed under vacuum to give a residue, which was purified by column chromatography on silica gel using hexanes/ethyl acetate as eluent (2/1,v/v) to give the second crop of 6 (0.14 g, 0.85 mmol, 57%).

5-Hydroxy-2,1-benzisoxazole (7).\(^1\)\(^6\) To a solution of stannous chloride dihydrate (27.08 g, 120.00 mmol) in concentrated hydrochloric acid (72 ml) cooled to 10-15 °C was added 2-nitro-5-hydroxybenzaldehyde (5.02 g, 30.00 mmol) with rapid stirring. After 135 min the mixture was diluted with water (135 ml) and extracted with ether (3×200 ml). The extract was neutralized (to pH 7) by successive washing with 5% aqueous sodium bicarbonate solution (2×150 ml) and brine (150 ml), then dried over anhydrous magnesium sulfate and concentrated to give a yellow solid, which was flash chromatographed through silica gel, eluting with hexanes/ethyl acetate (5/1, v/v) to give 7 as prisms (3.68 g, 27.2 mmol, 90%), mp 150-152 °C (lit.\(^1\) 150-152 °C).

2,1-Benzisoxazole-4,5-dione 4-(N-phenylhydrazone) (8). A solution of aniline (0.69 g, 7.4 mmol) in water (2.3 ml) and conc. HCl (2.3 ml) was cooled below 5 °C and a solution of sodium nitrite (0.56 g, 8.04 mmol) in water (4.6 ml) was added slowly with stirring at 0-5 °C. The solution of benzene diazonium chloride was then added in small portions at 0-5 °C to a solution of 5-hydroxy-2,1-benzisoxazole 7 (1.0 g, 7.4 mmol) in ethanol (70 ml) containing sodium hydroxide (1.11 g, 27.8 mmol). The mixture was stirred for 4 h at 0-5 °C after addition of the
diazonium chloride and was then neutralized to pH 7.5 with ethanoic acid. The solvent mixture was evaporated at 32 °C to leave a residue that was redissolved in water (70 ml) and the solution extracted with ether (3×70 ml). The combined extracts were dried (MgSO₄) and the extraction procedure repeated with the addition of a further 25 ml of ethanoic acid to the mother liquor. The resultant total of 1.84 g of crude product was then chromatographed on silica gel using hexanes/ethyl acetate as eluent to give 8 (1.61 g, 6.73 mmol, 91%) as purple prisms, mp 153-155 °C. ¹H NMR δ 6.75 (d, J = 9.9 Hz, 1H), 7.19 (t, J = 7.1 Hz, 1H), 7.36-7.52 (m, 4H), 7.67 (d, J = 9.9 Hz, 1H), 8.87 (s, 1H), 15.29 (br. s, 1H); ¹³C NMR δ 116.3 (2/C₆H), 116.7 (Cₒ), 124.2 (Cₒ), 125.8 (CH), 128.1 (CH), 129.6 (2/CH), 134.3 (CH), 141.6 (Cₒ), 151.1 (CH), 154.3 (Cₒ), 180.4 (C=O). Anal. Calcd for C₁₃H₉N₃O₂: C, 65.27; H, 3.79; N, 17.56. Found: C, 65.28; H, 3.76; N, 17.52.

General procedure for the preparation of (9, 10)
The azo coupling procedure for the preparation of (9, 10) was essentially the same and is exemplified by the preparation of 4-[(E)-2-phenyldiazenyl]-5-(1-pyrrolidinyl)-2,1-benzisoxazole (10). A solution of benzenediazonium chloride (1.6 mmol) was prepared as described for the preparation of (8) and was added in small portions at 0-5 °C to a solution of 5d, (0.3 g, 1.6 mmol) in ethanol (15 ml) containing sodium hydroxide (0.24 g, 6 mmol) and stirring continued for 4.5 h at 0-5 °C. The solvent was removed under vacuum and the residue was chromatographed on silica gel using hexanes/ethyl acetate (6/1, v/v) as eluent to give 10 (0.24 g, 0.82 mmol, 51%) as purple prisms, mp 150-151 °C. ¹H NMR δ 2.05-2.10 (m, 4H), 3.90-3.95 (m, 4H), 7.26 (d, J = 9.6 Hz, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 7.59 (d, J = 9.6 Hz, 1H), 7.72 (d, J = 7.7 Hz, 2H), 9.89 (s, 1H); ¹³C NMR δ 25.9 (2/C₆H₂), 53.8 (2/NC₆H₂), 110.6 (Cₒ), 120.8 (CH), 121.6 (2/CH), 125.3 (Cₒ), 127.0 (CH), 128.9 (2/CH), 145.2 (Cₒ), 153.4 (Cₒ), 154.1 (Cₒ), 155.6 (CH). Anal. Calcd for C₁₇H₁₆N₄O: C, 69.85; H, 5.52; N, 19.16. Found: C, 69.92; H, 5.56; N, 19.07.

5-(N,N-Dimethylamino)-4-[(E)-2-phenyldiazenyl]-2,1-benzisoxazole (9). Yield 13%, purple plates, mp 74-75 °C. ¹H NMR δ 3.48 (s, 6H), 7.31 (d, J = 9.9 Hz, 1H), 7.33 (t, J = 7.7 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 7.61 (d, J = 9.9 Hz, 1H), 7.79 (d, J = 7.7 Hz, 2H), 9.82 (s, 1H); ¹³C NMR δ 45.7 (2/NCH₃), 110.7 (Cₒ), 120.5 (CH), 121.8 (2/CH), 125.8 (Cₒ), 127.2 (CH), 128.6 (CH), 129.0 (2/CH), 148.8 (Cₒ), 153.8 (Cₒ), 153.9 (Cₒ), 155.9 (CH). HRMS (FAB) m/z Calcd for C₁₅H₁₄N₄O: 267.1246. Found: 267.1236.

References


