A Direct Preparation of 3-Hydroxy-1,2-benzisoxazoles

R. Friary and B. R. Sunday*

Research Division, Schering-Plough Corporation, Bloomfield, N. J. 07003

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Carbonyldiimidazole cyclizes 2-hydroxybenzohydroxamic acids to 3-hydroxy-1,2-benzisoxazoles.

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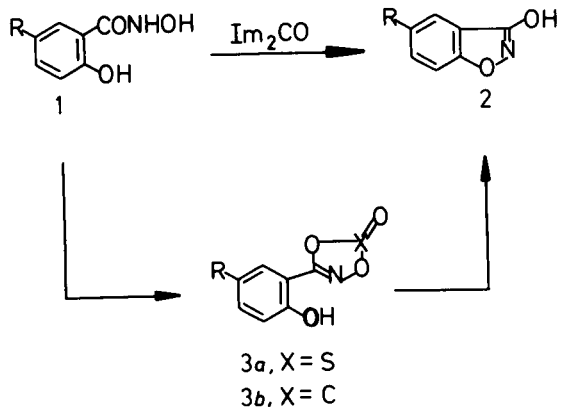
Cyclodehydration of 2-hydroxybenzohydroxamic acids (**1**) gives 3-hydroxybenzisoxazoles (**2**) in two stages (1,2). Under necessarily acidic conditions, thionyl and carbonyl chlorides change **1** to **3a** and **3b**, respectively, and bases like triethylamine and pyridine then convert **3a-b** to **2** (1,2).

These facts imply that **2** might be prepared directly if **1** could be changed to **3b** under basic conditions. Were any substituent of **1** oxidizable, they suggest that another reagent might yield more of **3** -- and hence of **2** -- than thionyl chloride.

Indeed, **3b** (R = CH_3CO) was formed when **1c** (R = CH_3CO) was treated at room temperature with 1.1 equivalents of carbonyldiimidazole, and brief treatment of **1a-b** with 2 equivalents of this reagent in hot tetrahydrofuran followed by acidification gave the corresponding, known 3-hydroxybenzisoxazoles **2a** (R = Cl, 68%) and **2b** (R = OMe, 42%). Although **2c** (R = CH_3CO) could not be prepared with thionyl chloride and triethylamine, carbonyldiimidazole and **1c** similarly yielded 95% of **2c**.



3a, X = S
3b, X = C

EXPERIMENTAL (3)

5-Chloro-2-hydroxybenzohydroxamic Acid (**1a**).

This compound, m.p. 231-232° (lit. m.p. 325° (1), m.p. 246° (4)), was prepared according to Böshagen (1).

2-Hydroxy-5-methoxybenzohydroxamic Acid (**1b**).

This compound, m.p. 172-175° (lit. m.p. 185° (1)), was prepared according to Böshagen (1).

Methyl 5-Acetyl-2-hydroxybenzoate.

This compound, m.p. 55-60° (lit. m.p. 60-62° (5), m.p. 55° (6)), was prepared in a yield of 81% from methyl 2-hydroxybenzoate, aluminum chloride and acetyl chloride by a Friedel-Crafts reaction in tetrachloroethane.

Methyl 5-(1,1-Dimethoxy)-ethyl-2-hydroxybenzoate.

A solution of methyl 5-acetyl-2-hydroxybenzoate (50.2 g., 0.258 mole), trimethylorthoformate (42.2 ml.), *p*-toluenesulfonic acid monohydrate (100 mg.), and methanol (250 ml.) was boiled under reflux for 2 hours; it was cooled, and sodium bicarbonate (500 mg.) was added. The solvents were evaporated and the residue in ether was washed with 1*M* sodium bicarbonate solution, water, and brine. The solution was dried over sodium sulfate, filtered and evaporated. Distillation of the residue gave 54.6 g. (88%) of the desired product, b.p. 96-104° at 0.15 mm. Crystallization from hexanes gave the analytical sample, m.p. 40-41°.

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71%. Found: C, 60.03; H, 6.70%.

5-Acetyl-2-hydroxybenzohydroxamic Acid (**1c**).

A. From Methyl 5-(1,1-Dimethoxy)-ethyl-2-hydroxybenzoate.

According to the method of Böshagen (1), this compound (0.23 mole) gave 93% of **1c**, identified by comparison of its ir spectrum to that of an authentic sample; deketalization occurred during work-up with aqueous hydrochloric acid.

B. From 2-Hydroxybenzohydroxamic Acid.

Acetyl chloride (21.4 g., 0.329 mole) was added dropwise to a stirred solution of aluminum chloride (57.5 g., 0.432 mole) in nitrobenzene (200 ml.) at 25°; the mixture was then stirred at 25° for 0.5 hour. In five equal portions, a total of 25.0 g. (0.163 mole) of 2-hydroxybenzohydroxamic acid was added during 1 hour; the internal temperature was kept at 20 to 30° by ice cooling. After 3 hours at 20°, the solution was added dropwise to ice water (1.6 kg.); the precipitate (29.6 g., m.p. 157-163° dec.) was collected, dried and crystallized from acetic acid to give 8.10 g. (25.5%) of the desired product, m.p. 213-217° dec. as a pink solid. Recrystallization from methanol gave the analytical sample.

Anal. Calcd. for $C_9H_9NO_4$: C, 55.39; H, 4.65; N, 7.18%. Found: C, 55.60; H, 4.75; N, 7.20%.

5-Acetyl-3-hydroxy-1,2-benzisoxazole (**2c**).

A solution of carbonyl diimidazole (62.0 g., 0.380 mole) in tetrahydrofuran (550 ml.) was added to a boiling solution of **1c** (37.0 g., 0.190 mole) in tetrahydrofuran (385 ml.); the resulting solution was then boiled under reflux for 1 hour and was cooled and evaporated. The residue was dissolved in water (330 ml.), and the solution was cooled and acidified to *p*H 2 with concentrated hydrochloric acid (100 ml.). The precipitate was collected and crystallized from ethyl acetate (using a Soxhlet extractor overnight) to give 30.0 g. (89%) of the desired

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product, m.p. 217.0-219.5°, as white needles. Two recrystallizations of the residue gave an additional 1.92 g., m.p. 212-216°, raising the yield to 95%; ^{13}C-nmr (DMSO-d_6): (25 MHz.) δ C_3, 167.0; C_{3a} 115.0; C_4, 123.3*; C_5, 132.6; C_6, 130.3*; C_7, 110.3; C_{7a}, 165.3; *C*O, 190.0; *C*H$_3$, 26.7 ppm

Anal. Calcd. for $C_9H_7NO_3$: C, 61.02; H, 3.98; N, 7.91. Found: C, 61.31; H, 3.92; N, 7.88.

3(5-Acetyl-2-hydroxyphenyl)-1,4,2-dioxazolin-2-en-5-one (**3b**, R = CH_3CO).

When **1c** was treated at room temperature with only 1.1 equivalents of carbonyldiimidazole in tetrahydrofuran, a small amount of **3b** (R = CH_3CO), m.p. 186-188°, was isolated instead of **2c**.

Anal. Calcd. for $C_{10}H_7NO_5$: C, 54.31; H, 3.19; N, 6.33. Found: C, 54.14; H, 2.97; N, 6.30.

Attempted Conversion of **1c** to **2c** with Thionyl Chloride.

In each of three trials, sequential treatment of **1c** with thionyl chloride and triethylamine according to Böshagen's method (1) gave an intractable mixture.

5-Chloro-3-hydroxy-1,2-benzisoxazole (**2a**).

Treatment of **1a** with two equivalents of carbonyldiimidazole in boiling tetrahydrofuran as described for **2c** gave, after crystallization from methanol, 68% of **2a**, m.p. 216-220° (lit. m.p. 220° (1)); ^{13}C-nmr (DMSO-d_6): (25 MHz) δ C_3, 165.0; C_{3a}, 116.3; C_4, 120.8*; C_5, 127.5; C_6, 130.6*; C_7, 111.8; C_{7a}, 162.0 ppm.

Anal. Calcd. for $C_7H_4ClNO_2$: C, 49.58; H, 2.38; Cl, 20.91; N, 8.26. Found: C, 49.55; H, 2.20; Cl, 20.88; N, 8.38.

3-Hydroxy-5-methoxy-1,2-benzisoxazole (**2b**).

Treatment of **1b** with two equivalents of carbonyldiimidazole in boiling tetrahydrofuran as described for **2c** gave, after crystallization from methanol, 42% of **2b**, m.p. 175-177° (lit. m.p. 183° (1)).

Anal. Calcd. for $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.48. Found: C, 57.90; H, 4.01; N, 8.52.

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(3) Melting points were determined on a Mel-Temp or a hot-stage apparatus and are uncorrected. E. Merck supplied F-254 silica gel plates for thin-layer chromatography. All products described in the experimental section were characterized by ir, pmr, and mass spectra. ^{13}C-nmr spectra were recorded on a Varian CFT-20 instrument.

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