Convenient Preparation of 2-Benzoxazolinones with 1,1-Carbonyldiimidazole

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A convenient and general preparation of 2-benzoxazolinones from 2-aminophenols with 1,1-carbonyldiimidazole is described. Included is a discussion of a much improved synthesis of the reproductive-stimulant 6-methoxy-2-benzoxazolinone (6-MBOA) that utilizes this procedure.

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6-Methoxy-2-benzoxazolinone (6-MBOA) **2c**, isolated from extracts of corn, wheat, and other grasses (1), has recently been reported to stimulate reproductive activity in the montane meadow vole (*Microtus montanus*) (2a-b). In addition, both 6-MBOA and naturally-derived 6,7-dimethoxy-2-benzoxazolinone (6,7-DMBOA) **2e** have been shown (3) to possess the property of modifying the binding affinity of auxins to receptor sites in corn (*Zea mays*).

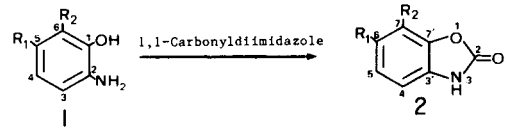
Unfortunately, previously reported syntheses of 6-MBOA and 6,7-DMBOA produce low overall yields (11-18%), from commercially available *m*-methoxyphenol (4,5,6,7), and from 2,3-dimethoxyphenol (<1%) respectively (8). The most successful of these syntheses utilizes a high temperature (140-180°) urea fusion as the final reaction with the appropriate *o*-aminophenol hydrochloride to form the benzoxazolinone ring (4,5,6). To effect a successful urea fusion reaction, the hygroscopic aminophenol hydrochloride generally should be dried thoroughly *in vacuo* after it is prepared, a procedure that can prove corrosive to an oil pump even when protected with a dry ice trap. The crude product obtained after workup is quite impure and requires crystallization first from water and several recrystallizations from dichloromethane (5) to prepare an analytically pure sample. Furthermore, the urea fusion is complicated by sublimation of urea and can produce erratic yields, particularly when carried out on a small scale (6).

Phosgene has also been frequently utilized in the formation of the benzoxazolinone ring from *o*-aminophenols (7,9) but is highly toxic and therefore inconvenient. Other reagents employed less frequently to prepare benzoxazolinones include carbonyl selenide (10a-b) and the corrosive ethyl chloroformate (11,12).

We wish to report a conveneint and general preparation of 2-benzoxazolinones from the reaction of *o*-aminophenols with readily available 1,1-carbonyldiimidazole, a reagent that has found previous utility in the preparation of benzimidazolinone and oxazolidinone ring systems (13). The preparation of 2-benzoxazolinones utilizing 1,1-carbonyldiimidazole has apparently not been previously described in the literature. The reaction can be conducted under relatively mild conditions (refluxing THF) and produces high yields of crystalline product (Table I). For example, yields of 73% and 95% were obtained for crystalline 6-MBOA (50% overall from *m*-methoxyphenol) and 6,7-DMBOA (22% overall from 2,3-dimethoxyphenol) respectively. In contrast to the urea fusion method, crude products are generally light colored and require only a single crystallization to yield pure material.

Table I

Preparation of Some 2-Benzoxazolinones With 1,1-Carbonyldiimidazole



1 2

Compound	R_1	R_2	Isolated as Yield
2a	H	H	97%
2b	$-CH_3$	H	75%
2c	$-OCH_3$	H	73%
2d	$-NO_2$	H	97%
2e	$-OCH_3$	$-OCH_3$	95%

EXPERIMENTAL

The cmr, pmr, ir and mass spectra were obtained using a JEOL JNM-PFT-100 (100 MHz), Nicolet 200 (200 MHz) or Varian EM-390 (90 MHz), Perkin-Elmer 727B and a Micromass 7070F spectrometer respectively. The cmr spectra were taken in deuteriodimethylsulfoxide and pmr spectra in deuteriochloroform with chemical shifts reported relative to tetramethylsilane unless otherwise indicated. Melting points are uncorrected

General Procedure for Benzoxazolinone Preparation.

To a solution of the appropriate aminophenol (30 mmoles) in 100 ml of anhydrous tetrahydrofuran was added 7.3 g of 1,1-carbonyldiimidazole (45 mmoles). The solution was refluxed on a steam cone for 4 hours. The tetrahydrofuran was removed *in vacuo* and the dry residue partitioned between 2*N* hydrochloric acid and chloroforom. The collected organic layer was treated with decolorizing carbon and dried with anhydrous sodium sulfate, stripped of solvent, and the residue crystallized from dichloromethane. In the preparation of compound **2d**, the initial residue from tetrahydrofuran was washed with 2*N* hydrochloric acid and crystallized from acetonitrile.

2-Benzoxazolinone (**2a**).

Compound **2a** was obtained as a white crystalline solid, mp 141.5° [lit (14) 142°]; ms: m/z (relative intensity) 135.0324 [Calcd. for $C_7H_5NO_2$: 135.0320] (M^+, 100), 106 (3), 91 (20), 79 (64); ir (potassium bromide): 1740 cm^{-1} (C=O); pmr (90 MHz) δ 7.2 (overlap of H-4 through H-7); cmr: δ 154.4 (C-2), 143.4 (C-7'), 130.4 (C-3'), 123.6 (C-5), 121.7 (C-6), 109.7 (C-7 or C-4), 109.4 (C-4 or C-7).

Anal. Calcd. for $C_7H_5NO_2$: C, 62.26; H, 3.73; N, 10.37. Found: C, 62.29; H, 3.71; N, 10.38.

6-Methyl-2-benzoxazolinone (**2b**).

Compound **2b** was obtained as colorless flat crystals, mp 145-146°; [lit (14) 145-146°]; ir (potassium bromide): 1745 cm^{-1} (C=O); ms: m/z (relative intensity), 149.0472 [Calcd. for $C_8H_7NO_2$: 149.0476] (M^+, 100), 148 (90), 120 (7), 107 (15), 106 (20), 105 (10), 104 (80); pmr: (200 MHz) δ 2.38 (s, CH_3, 3H), 6.95 (3H, overlap of H-4, H-5, and H-7), 9.8 (s, H-3, 1H, broad and deuterium oxide exchangeable); cmr (deuteriodimethylsulfoxide + chromium acetylacetonate): δ 154.5 (C-2), 143.4 (C-7'), 131.2 (C-3'), 127.8 (C-6), 124.4 (C-5), 109.9 (C-7 or C-4), 109.3 (C-4 or C-7), 20.9 (CH_3).

Anal. Calcd. for $C_8H_7NO_2$: C, 64.46; H, 4.73; N, 9.40. Found: C, 64.27; H, 4.67; N, 9.55.

6-Methoxy-2-benzoxazolinone (**2c**).

Compound **2c** was obtained as colorless needles, mp 154° [lit (1c) 154-155°]; ir (potassium bromide): 1750 cm^{-1} (C=O), 1610 cm^{-1} (C=C); ms: m/z (relative intensity) 165.0428 [Calcd. for $C_8H_7NO_3$: 165.0426] (M^+, 100), 150 (M^+-CH_3, 39), 122 (6), 109 (7), 106 (19); pmr: (200 MHz) δ 3.81 (s, OCH_3, 3H), 6.77 (d of d, H-5, 1H, $J_{5,4}$ = 8.6 Hz, $J_{5,7}$ = 2.4 Hz), 6.91 (d, H-7, 1H, $J_{7,5}$ = 2.4 Hz), 7.00 (d, H-4, 1H, $J_{4,5}$ = 8.6 Hz), 9.19 (s, H-3, 1H, deuterium oxide exchangeable); cmr: δ 155.1 (C-2 or C-6) 154.7 (C-6 or C-2), 144.0 (C-7'), 123.6 (C-3'), 109.8 (C-5 or C-4), 109.1 (C-4 or C-5), 55.7 (CH_3).

Anal. Calcd. for $C_8H_7NO_3$: C, 58.22; H, 4.27; N, 8.49. Found: C, 58.09; H, 4.27; N, 8.53.

6-Nitro-2-benzoxazolinone (**2d**).

Compound **2d** was obtained as pale yellow needles, mp 145-146° [lit (15) 146°]; ir (potassium bromide): 1780 cm^{-1} (C=O), 1605 (C=C); ms: m/z (relative intensity) 180.0172 [Calcd. for $C_7H_4N_2O_4$: 180.0171] (M^+, 100), 164 (5), 150 (16), 149 (6), 134 (21), 122 (5), 106 (33); pmr (deuteriodimethylsulfoxide): (200 MHz) δ 7.36 (d of d, H-4, 1H, $J_{4,5}$ = 8.5 Hz, $J_{4,7}$ = 0.2 Hz), 8.10 (d of d, H-7, 1H, $J_{7,4}$ = 0.2 Hz, $J_{7,5}$ = 2.1 Hz), 8.17 (d of d, H-5, 1H, $J_{5,4}$ = 8.5 Hz, $J_{5,7}$ = 2.1 Hz); cmr: δ 154.2 (C-2), 142.8 (C-7' or C-6), 142.1 (C-6 or C-7'), 130.8 (C-3'), 120.7 (C-5), 109.3 (C-4),105.3 (C-7).

Anal. Calcd. for $C_7H_4N_2O_4$: C, 46.70; H, 2.24; N, 15.56. Found: C, 46.81; H, 2.26; N, 15.29.

6,7-Dimethoxy-2-benzoxazolinone (**2e**).

Compound **2e** was obtained as colorless needles, mp 180-180.5° [lit (8) 180-181°]; ir (potassium bromide): 1750 cm^{-1} (C=O), 1601 cm^{-1} (C=C); ms: m/z (relative intensity) 195.0526 [Calcd. for $C_9H_9NO_4$: 195.05310] (M^+, 100), 181 (5), 180 ($M^+ - CH_3$, 61), 170 (2), 152 (4), 134 (11), 121 (8), 106 (3); pmr (deuteriomethanol): (200 MHz) δ 3.81 (s, 7-OCH_3, 3H), 4.02 (s, 6-OCH_3, 3H), 6.67 (d, H-4 or H-3, 1H, $J_{4,3}$ = 8.0 Hz), 6.82 (d, H-3 or H-4, 1H, $J_{4,3}$ = 8.0 Hz); cmr: δ 154.3 (C-2), 147.0 (C-7'), 134.7 (C-6), 133.2 (C-7), 125.4 (C-3), 108.4 (C-5), 102.6 (C-4), 60.2 (7-OCH_3 or 6-OCH_3), 56.7 (6-OCH_3 or 7-OCH_3).

Anal. Calcd. for $C_9H_9NO_4$: C, 55.42; H, 4.62; N, 7.18. Found: C, 55.25; H, 4.62; N, 7.14.

2-Amino-5-methoxyphenol (**1c**).

The procedure of Allen and Laird (4), in modified form, was used to prepare crystalline **1c** from *m*-methoxyphenol (Aldrich Chemical Co.), mp 128-129.5° [lit (16) 128-130°]; ms: m/z (relative intensity): 139.0632 [Calcd. for $C_6H_9NO_2$: 139.0633] (M^+, 87), 137 (39), 124 ($M^+ - CH_3$, 100), 109 (81), 108 (11); pmr (deuteriomethanol): (90 MHz) δ 3.64 (s, OCH_3, 3H), 6.30 (d, of d, H-4, 1H, $J_{4,3}$ = 6 Hz, $J_{4,6}$ = 3 Hz), 6.35 (d, H-6, 1H, $J_{6,4}$ = 3 Hz), 6.72 (d, H-3, 1H, $J_{3,4}$ = 6 Hz); cmr (deuteriomethanol): δ 156.3 (C-5), 148.5 (C-1), 126.5 (C-2), 119.4 (C-4), 105.6 (C-3), 103.0 (C-6), 56.0 (OCH_3). This compound could be stored in a dessicator under Argon for several weeks in the refrigerator.

2-Nitro-5,6-dimethoxyphenol and 2-Amino-5,6-dimethoxyphenol (**1e**).

The nitration procedure of Baker and Smith (17) was used to prepare crystalline 2-nitro-5,6-dimethoxyphenol from 2,3-dimethoxyphenol (Aldrich Chemical Co.), mp 100-101.5° [lit (17) 102-103°]; ms: m/z (relative intensity) 199.0480 [Calcd. for $C_8H_9NO_5$: 199.0481] (M^+, 100), 182 (97), 181 (41), 156 (13), 139 (29), 109 (10); pmr (deuteriodimethylsulfoxide): (200 MHz) δ 3.77 (s, 5-OCH_3, 3H), 3.94 (s, 6-OCH_3, 3H), 6.77 (d, H-4, 1H, $J_{4,3}$ = 9.0 Hz), 7.82 (d, H-3, 1H, $J_{3,4}$ = 9.0 Hz); cmr: δ 158.3 (C-5), 148.1 (C-1), 136.9 (C-6), 130.3 (C-2), 121.3 (C-3), 60.3 (6-OCH_3 or 5-OCH_3), 56.4 (5-OCH_3 or 6-OCH_3). Also isolated from the nitration product mixture was 1,3-dinitro-4,5-dimethoxyphenol; mp 76° [lit (17) 76°]; pmr (deuteriomethanol): (90 MHz) δ 3.47 (s, H-3, 1H), 3.86 (s, 5-OCH_3, 3H, broadened by restricted rotation--warming to 60° significantly sharpened this signal relative to the other two), 3.91 (s, 6-OCH_3, 3H); cmr: δ 152.7 (C-1 and C-5), 147.8 (C-6), 133.3 (C-2), 130.5 (C-5), 121.6 (C-4), 62.2 (5-OCH_3), 61.1 (5-OCH_3 or 6-OCH_3).

Compound **1e** was prepared in 60% yield by reduction of 2-nitro-5,6-dimethoxyphenol according to the procedure reported by Nielson *et al.* (18) and was used immediately to form **2e** due to its extreme susceptibility to air oxidation.

2-Aminophenol (**1a**), 2-Amino-5-nitrophenol) (**1d**) and 2-Amino-5-methylphenol (**1b**).

Both **1a** and **1d** were purchased from Aldrich Chemical Co. and ICN Pharmaceuticals, Inc., respectively. Compound **1b** was prepared by reduction of 2-nitro-5-methylphenol (Aldrich Chemical Co.) with sodium borohydride and 5% palladium on carbon according to the procedure reported by Nielson *et al.* (18) in 90% yield, mp 148-150° [lit (19) 148-150°]; ms: m/z (relative intensity) 123 (M^+, 100), 122 (81), 106 (20), 94 (13); pmr (deuteriomethanol): (200 MHz) δ 2.15 (s, CH_3, 3H), 6.45 (d of d, H-4, 1H, $J_{4,3}$ = 7.8 Hz, $J_{4,6}$ = 1.4 Hz), 6.53 (s, H-6, 1H), 6.63 (d, H-3, 1H, $J_{3,4}$ = 7.8 Hz); cmr (deuteriomethanol): δ 144.6 (C-1), 132.7 (C-2), 126.4 (C-5), 120.0 (C-4), 115.6 (C-3 or C-6), 115.4 (C-6 or C-3), 20.6 (CH_3).

Anal. Calcd. for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.51; H, 7.39; N, 11.39.

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