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TOTAL SYNTHESIS OF 4-ACETYLBENZOXAZOLIN-2-ONE

DAVID A. FIELDER*

Plant Research Centre

and F. WILLIAM COLLINS

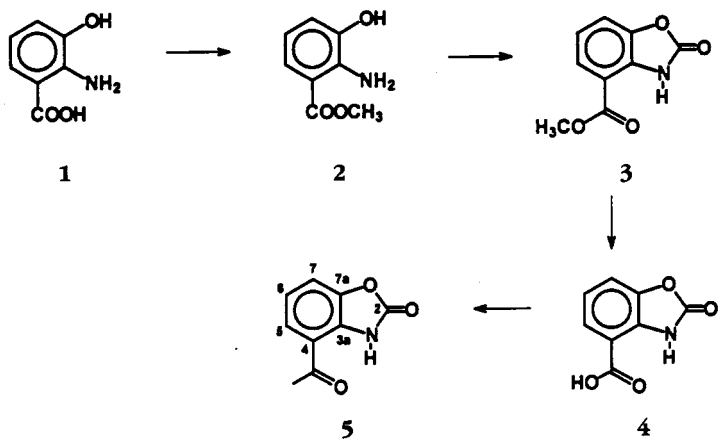
Centre for Food and Animal Research, Agriculture Canada, Ottawa, Ontario, Canada, K1A 0C6

ABSTRACT.—A practical synthesis of 4-acetylbenzoxazolin-2-one (4-ABOA) [**5**] in four steps and 57% overall yield, starting from 3-hydroxyanthranilic acid, is reported.

Recently, we reported the isolation and characterization of 4-acetylbenzoxazolin-2-one (4-ABOA, **5**), a biosynthetically novel benzoxazolin-2-one (1) from the kernels of a hybrid line of *Zea mays* that exhibits resistance to *Fusarium graminearum* (2). Due to the complex isolation and the low concentration of **5** found in kernels, a synthesis was required to produce sufficient quantities for assessing its biological activity. Both the 5- and 6-acyl synthetic analogues have been shown to possess analgesic, anti-inflammatory, and other pharmacological properties (3). Synthesis of these compounds follows a Friedel-Crafts acylation of benzoxazolin-2-one, which is commercially available (4). However, due to the para-directing nature of the aromatic ring substituents, this route was not possible for the synthesis of **5**.

The three known naturally occurring benzoxazolin-2-ones (5–7) possess antifungal (8) and anti-inflammatory properties (9), as well as conveying resistance against certain insects (10). Synthesis of these compounds has thus far required the formation of a heterocyclic ring from a substituted phenol to produce the benzoxazolin-2-one. In the syntheses of benzoxazolin-2-one (BOA), 6-methoxy- (MBOA), and 6,7-dimethoxybenzoxazolin-2-one (M_2BOA), the heterocyclic ring was formed via a Curtius rearrangement (11), or the reaction of urea (12), or phosgene (13) with the corresponding aminophenol.

Scheme 1 illustrates our synthetic sequence starting from 3-hydroxyanthranilic acid [**1**]. Prior to the formation of the heterocyclic ring, the reactive carboxylic acid was protected as the me-



SCHEME 1. Synthesis of 4-acetylbenzoxazolin-2-one (4-ABOA, **5**) from 3-hydroxyanthrinilic acid [**1**].

thyl ester [**2**] using H_2SO_4 in MeOH to prevent the formation of an isatoic anhydride or self-condensation product. The methyl ester **2** was treated with phosgene to form 4-carboxymethylbenzoxazolin-2-one [**3**] in high yield (96%). After quantitative hydrolysis of the ester, the free acid [**4**] was reduced to the methyl ketone with sequential treatment by methyllithium and trimethylchlorosilane (14) at room temperature to produce **5** (70%). The spectral data of synthetic **5** were identical with those previously reported (2). 4-Acetylbenzoxazolin-2-one [**5**] was formed from 3-hydroxyanthranilic acid in 57% overall yield.

EXPERIMENTAL

GENERAL EXPERIMENTAL PRCOEDURES.—Mps were determined on a Fisher-Johns melting point apparatus and are uncorrected. Uv spectra were taken on a Varian DMS200 spectrophotometer. Analytical tlc was performed on Si gel RP-18 (Whatman, 250 μm). Compounds were visualized by uv (365 nm) and with diethanolamine (5% w/v in EtOH). All moisture-sensitive reactions were conducted under a N_2 atmosphere in oven-dried glassware. Pyridine was distilled over CaH_2 and THF was distilled over sodium benzophenone ketyl prior to use. The sensitivity of compounds **1**, **2**, and **4** to light and air required all reactions to be performed in the dark and under a N_2 atmosphere. Mass spectra were obtained on a Finnigan gc/ms system, model 4500, with a DS 400 data system. Compound **5** was injected on-column and chromatographed on a DB-5 fused silica capillary column (20 m×0.32 mm i.d.; 0.25 μm film). The column was temperature programmed from 140 to 260° at 15°/min^{-1} with He as the carrier gas at 10 psi. ^{1}H- and ^{13}C-nmr spectra were run on a Bruker AM500 nmr spectrometer. Chemical shifts were referenced to MeOH-d_4 at 3.33 and 66.0 ppm for ^{1}H and ^{13}C, respectively, and reported relative to TMS.

METHYL-3-HYDROXYANTHRANILATE [**2**].—A suspension of 3-hydroxyanthranilic acid [**1**] (1.53 g, 10.0 mmol) in MeOH (200 ml) was heated until the acid went into solution. Then, H_2SO_4 (40 ml, concentrated) was added dropwise over 3 min and the resulting solution refluxed for 1.5 h. The solution was cooled and neutralized with a saturated $NaHCO_3$ (aqueous) solution. The orange solution was extracted with EtOAc (3×500 ml). The combined extracts were dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo*. Recrystallization from MeOH afforded pale orange crystals (1.42 g, 85% yield) of **2**: mp 95–97°; hrms *m/z* calcd for $C_8H_9NO_3$ 167.0582 ([M]$^+$, 100), observed 167.0596, 135 (85), 107 (97), 79 (18), 52 (16); ^{1}H nmr δ 3.85 (COO*CH*$_3$), 5.8 (br, OH), 6.48 (dd, H-5), 6.80 (d, H-3), 7.46 (d, H-2); ^{13}C nmr δ 51.6 (COO*CH*$_3$), 111.5 (C-1), 114.9 (C-5), 117.9 (C-4), 123.4 (C-6), 140.7 (C-2), 143.0 (C-3), 168.6 (*C*OOCH$_3$).

4-CARBOMETHOXYBENZOXAZOLIN-2-ONE [**3**].—Phosgene (6 ml, 20% in toluene; 11.6 mmol) was added at room temperature over 10 min to a stirred solution of **2** (1.22 g, 7.3 mmol) in pyridine (10 ml; dried over CaH_2). The mixture was allowed to stir overnight. The resulting pale orange solution was evaporated to dryness. The orange precipitate was dissolved in hot Me_2CO and filtered after being treated with decolorizing charcoal. After evaporation, the precipitate was recrystallized from Me_2CO/H_2O to afford **3** (1.36 g, 96% yield): mp 130–135° dec; hrms *m/z* calcd for $C_9H_7NO_4$ 193.0375 ([M]$^+$, 70), observed 193.0372, 161 (100), 133 (12), 105 (62), 77 (29), 51 (20); ^{1}H nmr δ 3.98 (COO*CH*$_3$), 7.20 (dd, $J_{6,7}=J_{6,5}=8.1$ Hz, H-6), 7.45 (dd, $J_{5,6}=8.0$ Hz, $J_{5,7}=1.1$ Hz, H-5), 7.75 (dd, $J_{7,6}=8.2$ Hz, $J_{7,5}=1.1$ Hz, H-7); ^{13}C nmr δ 156.7 (C-2), 132.9 (C-3a), 114.1 (C-4), 125.7 (C-5), 122.7 (C-6), 114.8 (C-7), 145.9 (C-7a), 166.5 (*C*OOCH$_3$), 52.7 (COO*CH*$_3$).

4-CARBOXYBENZOXAZOLIN-2-ONE [**4**].—A mixture of **3** (402 mg, 2.1 mmol) and 0.5 N NaOH (30 ml) was stirred for 1 h, until a clear colorless solution remained. The solution was then acidified with 1 N HCl and extracted with EtOAc. The solvent was evaporated to dryness to give a quantitative yield of **4**: hrms *m/z* calcd for $C_8H_5NO_4$ 179.0219, observed 179.0222, 161 (100), 105 (50), 77 (30), 51 (20); ^{1}H nmr δ 7.19 (dd, $J_{6,7}=J_{6,5}=8.1$ Hz, H-6), 7.42 (dd, $J_{5,6}=8.0$ Hz, $J_{5,7}=1.1$ Hz, H-5), 7.75 (dd, $J_{7,6}=8.2$ Hz, $J_{7,5}=1.1$ Hz, H-7); ^{13}C nmr δ 156.7 (C-2), 133.0 (C-3a), 115.4 (C-4), 126.0 (C-5), 122.6 (C-6), 114.4 (C-7), 145.8 (C-7a), 167.8 (*C*OOCH$_3$).

4-ACETYLBENZOXAZOLIN-2-ONE (4-ABOA, **5**).—MeLi (10 ml, 1.4 M in toluene) was added rapidly to a stirred solution of **4** (50 mg, 0.28 mmol) in dry THF (5 ml) at 0° under N_2. The resulting solution was stirred for 2.5 h at room temperature and then quenched with freshly distilled $(CH_3)_3SiCl$ (1000 μl). The solution was acidified with HCl (1 N, 3 ml) and stirred for 30 min. The solution was extracted with Et_2O, dried over $MgSO_4$, and dried *in vacuo*. The precipitate was taken up in *i*-PrOH-H_2O (1:1) and applied to a volume-calibrated column of Sephadex QAE (Pharmacia, Canada) in the hydroxide form and pre-equilibrated in *i*-PrOH-H_2O (1:1). Using this solvent, **5** eluted from the column in the first three

bed volumes. Compound **5** was recrystallized from MeOH/H_2O to give plate-like crystals (35 mg, 70%); hrms *m/z* calcd for $C_9H_7NO_3$ 177.0426, observed 177.0465. Its uv and nmr spectra and mp were in complete agreement with those of the natural compound (2).

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