# of 2(3*H*)-Benzoxazolones using Phenyl Chloroformate

Robert J. Maleski*, C. Edward Osborne and Sharon M. Cline

Organic Chemicals Division, Tennessee Eastman Company,
B-231, Kingsport, Tennessee 37662-5231

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2(3*H*)-Benzoxazolones **3** can be prepared directly from the corresponding 2-aminophenols and phenyl chloroformate. The intermediate 2-hydroxy phenylcarbamates **2** are formed easily in aqueous alcohol solvent and these are converted rapidly to product, without their isolation, using one equivalent of sodium hydroxide. The synthesis accommodates a wide variety of substituents, including the easily hydrolyzed ethyl ester.

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The most generally useful synthesis of 2(3*H*)-benzoxazolones **3**, compounds of medicinal and agricultural interest [1], involves the reaction of the appropriate 2-aminophenol with phosgene [1,3] or a phosgene equivalent. Our need for several simple derivatives of **3** (see Reaction Scheme) prompted a search for a safe, inexpensive, and simple method for converting **1** to **3**. Compatibility of the method with hydroxylic solvents, which are common media for the preparation of 2-aminophenols from the appropriate nitro compounds, was also highly desirable; many 2-aminophenols, especially those bearing electron donating substituents, are unstable in air, and are best reacted *in-situ* [4].

Urea at elevated temperatures [1,3] is a useful reagent for the preparation of the parent **3a** or for **3** bearing simple alkyl substituents, but the reaction conditions are too harsh for the preparation of thermally sensitive compounds such as **3d** or **3e**. Bis(trichloromethyl) carbonate [4] and 1,1-carbonyldiimidazole [5] are also effective, but they are expensive and may not be useful in the presence of protic solvents.

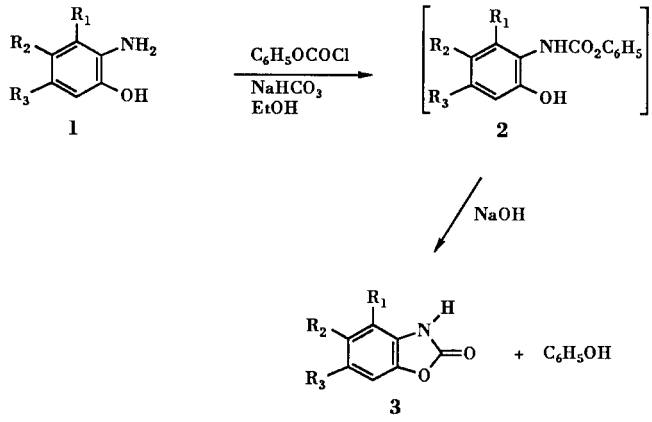
The chloroformate esters are inexpensive and safe phosgene equivalents, but the simple alkyl derivatives, when reacted with 2-aminophenols, yield alkyl phenylcarbamates which require high reaction temperatures [1] or catalysis [6] to affect ring closure. The aryl phenylcarbamates **2** are known to ring close spontaneously in high concentrations of aqueous potassium hydroxide [7], but these conditions cannot be used with easily hydrolyzed substituents. Moreover, it is not obvious that the aminophenols **1** can be cleanly converted to the appropriate phenylcarbamates **2** using phenyl chloroformate in a protic medium.

Results and Discussion.

We have found that phenyl chloroformate reacts rapidly and cleanly in 50% aqueous alcohol with a variety of simply substituted 2-aminophenols to produce intermediates **2a-g** (see Reaction Scheme) in high yield and good quality. The reaction is carried out at room temperature in the presence of one equivalent of sodium bicarbonate, and is complete in a matter of minutes. The selectivity of the reaction remains good even with the relatively non-nucleophilic aminophenols **1d** and **1e**.

The intermediates **2** precipitate soon after the additon of the phenyl chloroformate, but they need not be isolated. Simple addition of precisely one equivalent of aqueous sodium hydroxide to the slurries of **2** cleanly converts them to the corresponding **3**. The ring closure step is also complete in a matter of minutes, except for those compounds substituted with strong electron withdrawing substituents, **2d** and **2e**, which require a few hours for completion. Even with these, however, the entire operation can be carried out in four to five hours.

Reaction Scheme



Compound	R_1	R_2	R_3	Isolated Yield
3a	H	H	H	83 [a]
3b	H	CH_3	H	66 [a]
3c	H	H	CH_3	80 [a]
3d	H	NO_2	H	76 [a]
3e	NO_2	H	H	78 [a]
3f	H	CO_2Et	H	71 [a]
3g	H	H	OCH_3	70 [b]

Based on isolated 1. [b] Based on nitro precursor to 1g.

The Reaction Scheme details the compounds made by this procedure. The ring closure step in the absence of strong electron withdrawing substituents is obviously fast since the base-labile ethoxycarbonyl group of **3f** remained intact. The yields reported were not optimized. No impurities were observed in the isolated products, and two of them were isolated in such pure form that they gave satisfactory combustion analyses without subsequent purification.

This procedure accommodates a wide variety of electron donating and withdrawing substituents. The 6-methoxy compound **3g**, subject of significant interest as a naturally occurring pesticide, [4,6,8-10] can be conveniently prepared from the appropriate nitro compound without isolation of either **1g** or **2g**. This is especially important given the air sensitivity of **1g** [4].

The simplicity and speed of the conversions reported here constitute a valuable addition to the existing methods for the synthesis of 2(3*H*)-benzoxazolones. This method is of special importance in the preparation of large quantities of the subject compounds, where safety, economy, and time are of great importance.

EXPERIMENTAL

The ^{13}C nmr and ^{1}H nmr spectra were collected in DMSO-d_6 on a Varian model Gemini-300 spectrometer at frequencies of 75.5 and 300.1 Hz, respectively. Mass spectra were obtained on a Finnigan 4500 quadrupole mass spectrophotometer (70 eV). Infrared spectra (potassium bromide pellets) were collected on a Nicolet 5SXB Spectrophotometer.

Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Elemental analyses were performed by personnel of the Physical and Analytical Division of the Eastman Chemicals Company Research Laboratories. All starting materials were purchased from Aldrich: 2-aminophenol, 2-amino-3-nitrophenol, 3-methoxyphenol and ethyl 4-hydroxybenzoate were used as received; 2-amino-4-methylphenol and 2-amino-5-methylphenol were recrystallized from isopropyl alcohol; 2-amino-4-nitrophenol was recrystallized from ethyl acetate; 5-methoxy-2-nitrophenol [11] and ethyl-4-hydroxy-3-nitrobenzoate [12] were prepared by known procedure. All reactions were conducted under a positive atmosphere of nitrogen. All tlc analyses were conducted on Merck Kieselgel 60 glass plates using mixtures of ethyl acetate and heptane as developing solvents.

Ethyl 3-Amino-4-hydroxybenzoate (**1f**).

A mixture of 10.5 g (0.05 mole) of ethyl 4-hydroxy-3-nitrobenzoate, 100 ml of degassed ethanol, 0.4 g of 5% Pd on carbon and 12 g of ammonium formate was warmed in an inert atmosphere to 50° over 15 minutes. The reaction began to degas vigorously at about 40°. After 1 hour at 50° all the starting material had been consumed (tlc). The mixture was cooled, filtered through diatomaceous earth, and the crude product was concentrated *in vacuo*. The product was recrystallized from ethanol and water to give 4.8 g (53%) of white solid, mp 99-100° (lit [13] mp 96-99°); ir: 1690, 1710, 3300, 3390 cm^{-1}; ms: m/z 181 (M^+, 68), 153 (45), 136 (100), 108 (39), 80 (35); ^{1}H nmr: δ 1.28 (t, 3H, J = 7.1 Hz); 4.22 (q, 2H, J = 7.1 Hz); 6.72 (d, 1H, J = 8.2 Hz, H-5); 7.11 (dd, 1H, J = 2.0, 8.2 Hz, H-6); 7.25 (d, 1H, J = 2 Hz, H-2); ^{13}C nmr: δ 14.3, 59.9, 114.0, 115.1, 119.2, 121.4, 137.0, 149.1, 166.7.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.69; H, 6.13; N, 7.51. Found: C, 59.33; H, 6.07; N, 7.51.

2(3*H*)-Benzoxazolone (**3a**).

General Procedure.

A mixture of 10.9 g (0.1 mole) of 2-aminophenol, 50 ml of methanol, 50 ml of water, and 8.4 g (0.1 mole) of sodium bicarbonate was treated at 25-30° with 15.65 g (0.1 mole) of phenyl chloroformate, which was added over about 10 minutes. The resulting slurry of **2a** was stirred for 30 minutes and was treated dropwise, again at 25-30°, with a solution of 4 g (0.1 mole) of sodium hydroxide pellets in 50 ml of water. The resulting solution of product was acidified to about *p*H 5 (*p*H paper) with a solution of 10 g of concentrated hydrochloric acid in 50 ml of water. The resulting tan precipitate was collected by filtration and washed with water to give 11.2 g (83%) of **3a**, mp 139-140° (lit [14] mp 142-143°). All spectra were in accord with those previously reported [5].

5-Methyl-2(3*H*)-benzoxazolone (**3b**).

This compound had mp 131-132° (lit [15] mp 130-131°); ir: 1740, 1790 cm^{-1}; ms: m/z 149 (M^+, 100), 93 (41), 78 (23), 66 (25); ^{1}H nmr: δ 2.32 (s, 3H), 6.88 (dd, 1H, J = 0.7, 8 Hz, H-6), 6.90 (d, 1H, J = 0.7 Hz, H-4), 7.14 (d, 1H, J = 8 Hz, H-7); ^{13}C nmr: δ 21.0, 109.4, 110.5, 122.5, 130.8, 133.6, 141.9, 155.2.

Anal. Calcd. for $C_8H_7NO_2$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.35; H, 4.80; N, 9.25.

6-Methyl-2(3*H*)-benzoxazolone (**3c**).

This compound had mp 145-146° (lit [5] mp 145-146°). All spectra were in accord with those previously reported [5].

5-Nitro-2(3*H*)-benzoxazolone (**3d**).

This compound was prepared by the general procedure, but the ring closure of **2d** required 3 hours for completion (tlc), mp 227-229° (lit [16] mp 231-232°). A small sample was recrystallized from methanol to give a 91% recovery of a white solid, mp 229-230°; ir: 1340, 1520, 1740, 1780 cm^{-1}; ms: m/z 180 (M^+, 100), 150 (32), 134 (27), 106 (43), 78 (61), 51 (64); ^{1}H nmr: δ 7.54 (d, 1H, J = 8.8 Hz, H-7), 7.85 (d, 1H, J = 2.5 Hz, H-4), 8.06 (dd, 1H, J = 2.5, 8.8 Hz, H-6); ^{13}C nmr: δ 105.3, 110.2, 119.0, 131.7, 144.2, 148.4, 154.6.

Anal. Calcd. for $C_7H_4N_2O_4$: C, 46.64; H, 2.24; N, 15.55. Found: C, 46.44; H, 2.12; N, 15.31.

4-Nitro-2(3*H*)-benzoxazolone (**3e**).

This compound was prepared exactly as **3d** above, mp 229-231° (lit [17] mp 227-228°); ir: 1340, 1520, 1810 cm^{-1}; ms: m/z 180 (M^+, 64), 108 (63), 106 (75), 77 (100), 51 (50); ^{1}H nmr: δ 7.29 (t, 1H, J = 9 Hz, H-6), 7.73 (d, 1H, J = 8 Hz, H-7), 7.94 (d, 1H, H = 9 Hz, H-5); ^{13}C nmr: δ 115.8, 118.8, 121.9, 127.9, 131.6, 145.3, 154.5.

Anal. Calcd. for $C_7H_4N_2O_4$: C, 46.64; H, 2.24; N, 15.55. Found: C, 46.40; H, 2.21; N, 15.49.

5-Ethoxycarbonyl-2(3*H*)-benzoxazolone (**3f**).

This compound was prepared from **1f** by the general pro-

cedure, except that methanol was replaced with ethanol, mp 129-130°. A small sample was recrystallized from toluene to give an 85% recovery of white solid, mp 132-133°; ir: 1790, 1710 cm^{-1}; ms: m/z 207 (M^+, 29), 179 (26), 162 (100), 51 (21); ^1H nmr: δ 1.33 (t, 3H, J = 7.1 Hz), 4.32 (q, 2H, J = 7.1 Hz), 7.41 (d, 1H, J = 8.5 Hz, H-7), 7.57 (d, 1H, J = 1.6 Hz, H-4), 7.75 (dd, 1H, J = 1.6, 8.5 Hz, H-6); ^{13}C nmr: δ 14.2, 61.1, 109.8, 110.5, 124.3, 126.0, 131.2, 147.3, 154.7, 165.7.

Anal. Calcd. for $C_{10}H_9NO_4$: C, 57.96; H, 4.37; N, 6.76. Found: C, 57.84; H, 4.32; N, 6.56.

6-Methoxy-2(3*H*)-benzoxazolone (**3g**).

A nitrogen-degassed mixture of 3.06 g (0.02 mole) of 5-methoxy-2-nitrophenol, 50 ml of ethanol, 0.1 g of 5% palladium on carbon, and 3.79 g of ammonium formate was heated to 60° and held for 1 hour. Vigorous degassing was observed. Analysis by tlc indicated that all of the nitro compound had been consumed. The solvent and resulting ammonia were removed by a stream of nitrogen, and a previously degassed solution of 20 ml of ethanol and 20 ml of water was then added, followed by 1.65 g (0.02 mole) of sodium bicarbonate and 3.13 g (0.02 mole) of phenyl chloroformate. The resulting slurry was stirred 0.5 hour at room temperature and was treated with a solution of 0.8 g (0.02 mole) of sodium hydroxide in 10 ml of water. The mixture was filtered through diatomaceous earth to remove the catalyst and the product was precipitated by acidification with 10% hydrochloric acid to a *p*H (*p*H paper) of 5-7. The product was filtered to give 2.3 g (70%) of a white solid, mp 152-153° (lit [18] mp 153-154°). All spectra were consistent with those previously reported [5].

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