Synthesis of $^{14}$C Labeled 3-Methoxy-4-Hydroxy $\alpha$-(2-Methoxyphenoxy)-$\beta$-Hydroxypropiophenone, a Lignin Model Compound

By Lawrence L. Landucci, Sally A. Geddes, and T. Kent Kirk*)

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**Introduction**

In the study of microbial degradation of lignin it was of interest to complement investigations made with synthetic $^{14}$C-lignins (Kirk et al. 1975) with similar studies using $^{14}$C-labeled 3-methoxy-4-hydroxy-$\alpha$-(2-methoxyphenoxy)-$\beta$-hydroxypropiophenone, (structure (10) in Fig. 1).** However, previously published experimental methods were unsuitable for small-scale operations because of expensive losses in repeated extractions, transfers, and crystallizations. A modified synthesis was therefore devised based on the scheme illustrated in Figure 1, which was developed by others (Adler et al. 1952; Kratzl et al. 1959; and Kratzl and Vierhapper 1971).

Described here is the synthesis of uniformly A-ring-labeled (10) from commercially available [Ring-U-$^{14}$C]-phenol, via guaiacol (4) (Fig. 1). Procedures have been described by Kratzl and Vierhapper (1971) for preparing guaiacol labeled in specific ring carbons, thus making it possible to label the ring carbons of final product (10) more specifically, if desired. Labeling of the aliphatic carbons of (10) can also be accomplished readily by use of commercially available [$^{14}$C]-acetic acid or [$^{14}$C]-formaldehyde; the methoxyl position(s) can be specifically labeled by use of [$^{14}$C]-diazomethane.

Although most of the modifications described in this paper were made specifically to suit small-scale operations, they could be used advantageously in the large-scale synthesis of unlabeled (10) in Figure 1 starting from commercially available acetovanillone.

**Results and Discussion**

By the method of Kratzl and Vierhapper (1971), 2-(2-methoxyphenoxy)-5-nitrobenzophenone, (3) in Fig. 1,
was prepared from \([\text{Ring-}\text{U-}^{14}\text{C}]\)-phenol in an overall yield of about 90%. Upon refluxing of (3) in piperidines nucleophilic displacement of the guaiacoy moiety occurred, resulting in a crude oil which upon chromatographic purification on silica gel afforded \([\text{Ring-}\text{U-}^{14}\text{C}]\)-guaiacol (4) in 70% yield. A boron trifluoride catalyzed Friedel-Crafts acylation of (4) with acetic acid, followed by chromatographic purification on silica gel, gave \([\text{Ring-}\text{U-}^{14}\text{C}]\)-acetovanillone (5) in 56% yield (36% yield from phenol). This acylation was one of the lowest yield steps in the reaction sequence, so may warrant further optimization.

All subsequent steps in the synthesis required the use of a simple vacuum apparatus, as shown in Figure 2, which was devised to minimize the transfers leading to excessive material loss in small-scale operations.

The benzylation of acetovanillone (5) with benzyl bromide in the presence of potassium carbonate is a modification of the procedure described by Leopold (1950), and gave a 96% yield of product (6) which melted at 85° to 87°C.

The a-bromination of (6) required considerable modification for an acceptable yield free of byproducts. Although chloroform has been the solvent of choice in previous reports (Adler et al. 1952; Kratzl et al. 1959), it was found that carbon tetrachloride in the presence of a trace of chloroform resulted in a much cleaner reaction. During the bromination an intermediate separates from solution, possibly structure (12), resulting from the addition of molecular bromine across the double bond of the enol form (11) of (6) as illustrated in Figure 3. This unstable intermediate could lose hydrogen bromide to give (13), which would then rearrange to the stable keto form (7).

Chloroform initiates the decomposition of the intermediate (12). In the absence of a trace of chloroform the carbon tetrachloride suspension of the intermediate had to be heated longer and at a higher temperature in order to initiate decomposition; this step resulted in lower yields of poorer quality product (7). Although individual reactions varied somewhat, it was not difficult to obtain roughly
70% yield of white crystals which melted at 98° to 102 °C and were pure enough to proceed without recrystallization. In a separate experiment the intermediate bromohydrin (12) was filtered off (before chloroform addition) and air-dried, giving a yellow solid which decomposed at 81° to 85 °C with hydrogen bromide evolution. The infrared spectrum of (12) contained a broad hydroxyl absorption at 3350 cm⁻¹ and only a weak residual carbonyl absorption at 1665 cm⁻¹.

The nucleophilic displacement of the bromine atom in (7) by the guaiacol anion was relatively straightforward and required little modification from the literature procedure (Kratzl et al. 1959). The major change was that a stoichiometric amount of guaiacol was used in order to avoid the usual extraction operation to remove the unreacted excess. Numerous trials indicated that this reaction was relatively consistent, yielding over 90% of product (8) which melted at 96° to 101 °C and was sufficiently pure to proceed without recrystallization.

The condensation of formaldehyde with (8) in the presence of anhydrous potassium carbonate was similar to that previously reported for the synthesis of the veratryl analog of (10), [3,4-dimethoxy-α-(2-methoxyphenoxy)-β-hydroxypropiophenone] (Adler et al. 1952). This reaction was one of the most critical in the success since slight deviations from the reported conditions frequently resulted in the formation of an unidentified dehydrogenation product from which neither starting material nor desired product could be recovered. A temperature of 28° to 32 °C appeared to be critical to the success of the reaction. Also, absolute ethanol must not be substituted for the 95% ethanol as solvent since it has been shown in an independent experiment (Landucci 1973, unpublished results) that the desired product (9) is degraded rapidly when heated in absolute ethanol at 28° to 32 °C in the presence of potassium carbonate. Apparently, the absolute ethanol acted as a mild dehydrating agent under these conditions and resulted in the formation of the previously mentioned dehydrogenation product. With reasonable care an 80% yield of product melting at 102° to 106 °C could be obtained consistently.

The hydroxylation of (9) to (10) in the presence of palladium on charcoal was perhaps the most inconsistent step in the sequence. Many solvents and solvent mixtures were tried, but most resulted in partial or total reduction of the α-carbonyl group in addition to hydroxylation of the benzyl moiety. The most successful solvent system found was 10% aqueous tetrahydrofuran. This system yielded about 50% of very pure product (10) melting at 95° to 98.5 °C.

**Experimental**

Nuclear Magnetic Resonance spectra were determined on a Varian T-60 Spectrophotometer with tetramethylsilane as internal reference (6 = 0 ppm). All melting points are uncorrected. The identities of the compounds (4) through (10) were confirmed by spectrophotometric (IR and ¹H NMR) comparison with authentic samples.

**3-Methoxy-4-benzyloxyacetophenone (6)**

A mixture of acetovanillone (5) (600 mg, 3.61 mmoles), benzyl bromide (630 mg, 3.68 mmoles), and powdered potassium carbonate (500 mg, 3.63 mmoles), in anhydrous acetone (15 ml), was refluxed for 3 hours while stirring magnetically. The acetone portion was then separated from the potassium carbonate by means of a vacuum apparatus illustrated in Figure 2. The filtrate was evaporated under vacuum and the resulting crystals were washed several times with small amounts of cold petroleum ether. The ether washes were filtered off with the vacuum apparatus. (This device was also used in all subsequent filtration and washing operations.) The crystals were then dried at room temperature under vacuum (895 mg, 3.50 mmoles, 96% yield, m.p. 85°–87°C).

**3-Methoxy-4-benzyloxy-bromacetophenone (7)**

A mixture of acetovanillone (5) (600 mg, 3.61 mmoles), benzyl bromide (630 mg, 3.68 mmoles), and powdered potassium carbonate (500 mg, 3.63 mmoles), in anhydrous acetone (15 ml), was refluxed for 3 hours while stirring magnetically. The acetone portion was then separated from the potassium carbonate by means of a vacuum apparatus illustrated in Figure 2. The filtrate was evaporated under vacuum and the resulting crystals were washed several times with small amounts of cold petroleum ether. The ether washes were filtered off with the vacuum apparatus. (This device was also used in all subsequent filtration and washing operations.) The crystals were then dried at room temperature under vacuum (895 mg, 3.50 mmoles, 96% yield, m.p. 85°–87°C).
yellow and hydrogen bromide was given off. At this point the mixture was neutralized with a saturated sodium bicarbonate solution (25 –30 ml). The carbon tetrachloride phase was separated from the bicarbonate solution, dried with anhydrous magnesium sulfate, and evaporated under vacuum. Resulting crystals were washed several times with small amounts of cold methanol and then dried under nitrogen (810 mg, 2.42 mmoles, 69% yield, m.p. 98° –102 °C).

3-Methoxy-4-benzyloxy-α-(2-methoxyphenoxy)-acetophenone (8)

3-Methoxy-4-benzyloxy-α-bromoacetophenone (7) (810 mg, 2.42 mmoles), guaiacol (335 mg, 2.42 mmoles), and powdered potassium carbonate (300 mg, 2.42 mmoles) were refluxed in acetone (4 ml) for 4 hours. The acetone portion was separated from the potassium carbonate with the vacuum apparatus. As the compound had a tendency to bump when evaporated under vacuum, nitrogen was used to evaporate off the solvent. The resulting yellow crystals were washed five times with small portions of petroleum ether and dried under nitrogen (850 mg, 2.25 mmoles, 93% yield, m.p. 96°–101 °C).

3-Methoxy-4-benzyloxy-α-(2-methoxyphenoxy)-β-hydroxypropiophenone (9)

A mixture of 3-methoxy-4-benzyloxy-α-(2-methoxyphenoxy)-acetophenone (8) (850 mg, 2.52 mmoles), formaldehyde (0.4 ml of 37% solution, 150 mg, 4.9 mmoles), powdered anhydrous potassium carbonate (40 mg, 0.29 mmoles), and 95% ethanol (4.1 ml) was stirred magnetically while kept at a temperature of 30.5 °C ± 0.5 °C. The reaction was stopped when thin layer chromatography (silica gel, 20% ethyl acetate/cyclohexane) indicated that the mixture was almost entirely product, after approximately 8 hours. The mixture was then cooled in a freezer for 5 minutes and the ethanol removed by vacuum filtration. The solid was washed well with small portions of water to remove any remaining formaldehyde and potassium carbonate (740 mg, 1.81 mmoles, 80% yield, m.p. 102°–106 °C).

3-Methoxy-4-hydroxy-α-(2-methoxyphenoxy)-β-hydroxypropiophenone (10)

A mixture of 3-methoxy-4-benzyloxy-α-(2-methoxyphenoxy)-β-hydroxypropiophenone (9) (740 mg, 1.81 mmoles), 10% palladium on charcoal (Matheson, Coelmann and Bell, 120 mg), tetrahydrofuran (22 ml), and water (1.5 ml) was magnetically stirred under hydrogen (2 atmos). After approximately 20 minutes the pressure had dropped and remained constant. The mixture was filtered to remove the catalyst and the filtrate dried with anhydrous magnesium sulfate and evaporated under vacuum, leaving a gold-colored oil. A 1H NMR spectrum of the oil indicated a mixture of the desired product (10) (85 %), guaiacylglycerol-β-guaiacyl ether [1,3-methoxy-4-hydroxyphenyl)-2-(2-methoxyphenoxy)propan-1,3-diol] (12%), and a trace of starting material (9) (3%). The oil was triturated with a small amount of ether and left covered for a minimal 24-hour period before crystals formed. An additional small amount of ether was added to the semisolid and the resulting mixture filtered, leaving white crystals (274 mg, 0.86 mmoles, 48% yield) which melted at 95°–98.5 °C.

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References


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