On the Kolbe–Schmitt Synthesis of Pharmacologically Useful Salicylates: Carboxylation of 2,4-Di-*t*-butylphenol and Identification and Reduction of the Formation of 2,2′-Dihydroxy-3,3′,5,5′-tetra-*t*-butylbiphenyl in the Synthesis of 3,5-Di-*t*-butylsalicylic Acid

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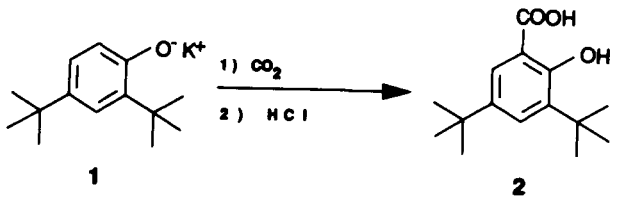
Abstract □ The initial yield of 3,5-di-*t*-butylsalicylic acid obtained via Kolbe–Schmitt carboxylation of the potassium salt of 2,4-di-*t*-butylphenol was <1% and was accompanied by a 65% yield of 2,2′-dihydroxy-3,3′,5,5′-tetra-*t*-butylbiphenyl, a dimer of the 2,4-di-*t*-butylphenol formed by ortho coupling of phenoxide radicals. Formation of this dimer was decreased to 8%, and the yield of 3,5-di-*t*-butylsalicylic acid was increased to 68% by optimizing reaction time and temperature and decreasing the amount of oxygen present during carboxylation. This modification of the Kolbe–Schmitt reaction conditions may be generally helpful in the synthesis of all pharmacologically useful salicylates.

Kolbe–Schmitt carboxylation of substituted phenols is a common means of synthesis of substituted salicylic acids.[1–6] Yields are generally high (60 to 80%), with reaction conditions described as heating an anhydrous alkali salt, with some preference for the potassium salt, of the phenol at 140 to 200 °C under 1 to 100 atm of CO_2 pressure for 4 to 8 h. Salicylic acids synthesized under these conditions are isolated by extracting the reaction mixture with water or an aqueous bicarbonate solution and precipitating following acidification. While many salicylic acids have been synthesized using Kolbe–Schmitt reaction conditions, perusal of *Chemical Abstracts* and *Beilstein's Handbuch der Organischen Chemie* revealed that 3,5-di-*t*-butylsalicylic acid had not been synthesized using these conditions.

The copper complex of 3,5-di-*t*-butylsalicylic acid was one of a series of copper salicylates found to have anticancer activity.[7–13] When additional quantities of this complex were needed to pursue this observation and study its mechanism of action, it was found that 3,5-di-*t*-butylsalicylic acid (2) was no longer commercially available. Because the 2-4-di-*t*-butylphenol (1) required for Kolbe–Schmitt synthesis of 2 was commercially available and inexpensive, we attempted the synthesis of 2 using Kolbe–Schmitt conditions as shown in Scheme I.

Kolbe–Schmitt carboxylation of potassium 2,4-di-*t*-butylphenoxide gave <1% of the expected product and a 65% yield of an unexpected product which was not soluble in saturated aqueous sodium bicarbonate. This report identifies this unexpected product as 2,2′-dihydroxy-3,3′,5,5′-tetra-*t*-butylbiphenyl, formed via ortho coupling of phenoxide radicals as shown below. Also, the exclusion of oxygen from the reaction vessel, as a modification of Kolbe–Schmitt reaction conditions, decreased the yield of the biphenyl to 8% and increased the yield of the desired salicylic acid to 68%. It may also be useful in increasing the yield of other expected Kolbe–Schmitt reaction products (see Scheme II).



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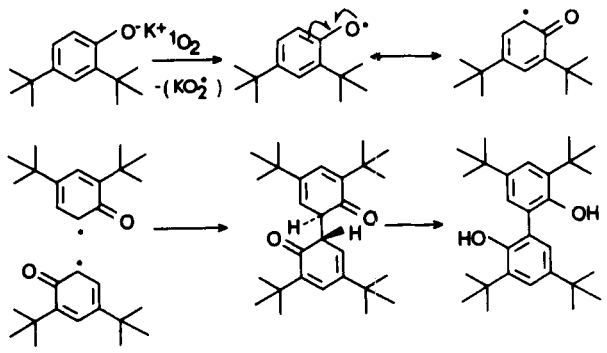
Scheme I

Experimental Section

Melting points were determined in a Thomas Hoover melting point apparatus using glass capillaries and are uncorrected. Elemental analyses (C,H) were done by MHW Laboratories, Phoenix, AZ, and agree with theoretical values within ±0.4%. The ^1H NMR spectra were obtained at ambient temperature (25–30 °C) with a Varian EM-360 spectrophotometer at 60 MHz. Chemical shifts are reported in parts per million (δ) downfield from an internal TMS standard. Ultraviolet spectra were determined in reagent grade ethanol using a Shimadzu-Spectronic 200 UV spectrophotometer. The pressure carboxylation of the potassium salt of 2,4-di-*t*-butylphenol was achieved in a Parr pressure reactor (model series 4000). Coleman dry CO_2 was admitted into the reactor at a pressure of 50–60 atm (750 to 900 psi).

Synthesis of Potassium 2,4-di-*t*-Butylphenolate—The 2,4-di-*t*-butylphenol (30.3 g, 0.145 mol) was dissolved in 250 mL of toluene in a three-necked flask fitted with a thermometer, paddle stirrer, and a Dean Stark trap with a condenser that was topped with a calcium sulfate drying tube. This solution was vigorously stirred using a motor-driven paddle stirrer. A KOH solution prepared by dissolving 9.57 g (85.1% assay) in 150 mL of absolute ethanol with warming at 50 °C was slowly dropped into a toluene solution of the phenol over a period of 2 h. The temperature of the reaction mixture was raised to reflux temperature, and the water and ethanol were removed by azeotropic distillation.

As the temperature reached 78 °C, the reaction mixture became wine red in color. As the distillation continued, toluene was added to the reaction vessel to maintain a volume of ~600 mL, to prevent an increase in viscosity, and to avoid caking. When the temperature approached 95 °C, the potassium phenoxide began to precipitate. On



Scheme II

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further heating to 110 °C, the boiling point of toluene, precipitation of the yellowish-white phenoxide increased. The reaction mixture was kept at reflux temperature for an additional hour and then allowed to cool with continued stirring.

To keep the hygroscopic phenoxide salt as dry as possible, it was collected by filtration using a large sintered-glass filter funnel in a plastic bag continuously purged with dry nitrogen (10 psi). The filtered salt was washed several times with sodium-dried diethyl ether (50 mL) to remove unreacted phenol and allowed to dry for 1 h in the filter funnel attached to a vacuum line (15 mmHg) in the nitrogen atmosphere. Further drying in a vacuum oven (15 mmHg and 50 °C) for ~12 to 18 h gave a yellowish-white solid (yield 32.5 g; 90.6%).

One-gram samples were systematically analyzed for stability over a period of 1 week by monitoring the amount of phenol recovered following the addition of the salt to acidic water and the formation of the biphenyl on drying at 50 °C. The 2,4-di-*t*-butylphenol (mp 54 °C) was characterized by NMR. This experiment demonstrated that the potassium phenoxide can be kept at 15 mmHg and 50 °C in a vacuum oven for up to 1 week without biphenyl formation.

Pressure Carboxylation—Anhydrous potassium 2,4-di-*t*-butylphenoxide (5 g, 20.5 mmol) was rapidly mixed with ~30 3-mm glass beads, to increase the surface area of the phenoxide, in a 100-mL round-bottomed flask which was then placed in the steel pressure reactor. After assembling the reactor, oxygen was removed by evacuation (0.1 μmHg for 1 h) or purged by passing nitrogen (15 psi) into the reactor for 15 min. If nitrogen was used, the reactor was purged with dry carbon dioxide at 15 psi for an additional 15 min. Finally, the reactor was pressurized to 850–900 psi with dry CO_2 and heated to the required temperature for the required time period. The reaction vessel was then allowed to cool, excess CO_2 was vented, and reaction products were isolated and characterized. The reaction mixture usually solidified to a reddish-brown mass, and unreacted phenol which co-distilled from the flask with the biphenyl into the reactor was recovered with ether. Relative concentrations of phenol and biphenyl were determined by NMR and percentage yields were calculated. The reaction mixture remaining in the flask was suspended in deionized water (100 mL) and extracted with two 25-mL portions of diethyl ether to remove any remaining unreacted phenol and/or the biphenyl. The aqueous layer was then acidified (pH 1.0) with concentrated HCl, and the 3,5-di-*t*-butylsalicylic acid was collected by filtration, dried, and weighed. The ether-soluble materials were combined, and the relative amounts of phenol and biphenyl were determined by NMR.

Analytical Data—*2,2'-Dihydroxy-3,3',5,5'-tetra-t-butylbiphenyl*—Anal. ($C_{28}H_{42}O_2$) C, H; mp 196 °C (lit.[8] 196–198 °C); ^{1}H NMR (CCl_4): δ 1.32 (18 H, s, *t*-Bu), 1.46 (18 H, s, *t*-Bu), 5.19 (2 H, s, exchangeable with D_2O, OH), 7.00 (2 H, d, $J \simeq 2.5$ Hz, ArH), and 7.37 (2 H, d, $J \simeq 2.5$ H 2, ArH); UV maxima (molar absorptivity) at 283 nm (6417 M^{-1} cm^{-1}) and 244 nm (9326 M^{-1} cm^{-1}).

3,5-Di-t-butylsalicylic Acid—Anal. ($C_{15}H_{22}O_3$) C, H; mp 164 °C (lit. 164 °C); ^{1}H NMR (CCL_4): δ 1.32 (9 H, s, *t*-Bu), 1.46 (9 H, s, *t*-Bu), 7.3 (1 H, d, $J \simeq 2.0$, ArH), 7.6 (1 H, d, $J \simeq 2.0$, ArH), 10.8 (1 H, s, OH), and 11.5 (1 H, s, COOH); UV maxima (molar absorptivity) at 317 nm (4737 M^{-1} cm^{-1}) and 246 nm (5965 M^{-1} cm^{-1}). In $(CD_3)_2CO$, the proton resonances for the hydroxyl and carboxyl protons were shifted to δ = 9.5 (1 H, s, OH) and 11.40 (1 H, s, COOH), respectively. The shift in deuterated acetone of ~1 ppm is attributed to intermolecular hydrogen bonding of the hydroxy group to the carbonyl oxygen of the carboxyl group.

Results and Discussion

Initially, Kolbe–Schmitt carboxylation of potassium 2,4-di-*t*-butylphenolate gave a 65% yield of a product which was soluble in diethyl ether and insoluble in saturated aqueous bicarbonate. This product was identified as 2,2'-dihydroxy-3,3',5,5'-tetra-*t*-butylbiphenyl based on elemental analyses, melting point, NMR spectrum, and UV spectrum. Carbon and hydrogen elemental analyses agreed within ±0.4% with the theoretical values calculated for $C_{28}H_{42}O_2$. A 196 °C melting point agreed with the value of 196–198 °C reported by Armstrong et al.[14] The ^{1}H NMR spectrum obtained in CCl_4 contained a singlet at 1.32 ppm for 18 hydrogens in the 3,3'-*t*-butyl groups, a singlet at 1.46 ppm for 18 hydrogens in the 5,5'-*t*-butyl groups, a singlet at 5.19 ppm for the two deuterium exchangeable hydrogens of the phenolic hydroxyl groups, and two sets of two doublets with coupling constants of ~2.5 Hz for four aromatic hydrogens. The UV spectrum contained two maxima, one at 283 nm with a molar absorptivity of 6417 M^{-1} cm^{-1} and the other at 244 nm with a molar absorptivity of 9326 M^{-1} cm^{-1}, consistent with non-coplanar and coplanar aromatic ring forms of this compound.

This biphenyl has been previously synthesized by Armstrong et al.[14] by thermal decomposition of di-*t*-butyl peroxide in the presence of 2,4-di-*t*-butylphenol via ortho–ortho coupling of phenoxide radicals. It is likely that the unexpected biphenyl was formed via air oxidation on heating of the phenoxide salt. Perusal of the Kolbe–Schmitt reaction literature[1–6] did not reveal any mention of an ortho–ortho coupled oxidation product.

The yield of this biphenyl was decreased from 65 to 10%, and the yield of salicylic acid increased from <1 to 50% by purging oxygen from the reaction vessel with nitrogen and then dry CO_2 prior to sealing and heating at 150 °C for 5 h. This reaction temperature and duration of heating were determined to produce this maximum yield of 65% in studies wherein the temperature was varied from 110 to 180 °C and duration of heating varied from 2.5 to 10 h. Decarboxylation of 3,5-di-*t*-butylsalicylic acid may account for lower yields when the reaction was performed at temperatures >150 °C and for durations >5 h.

The yield of substituted salicylic acid was further increased to 68% and the yield of substituted biphenyl decreased to 8% when the reaction vessel was evacuated at 0.1 μmHg for 1 h prior to admitting dry CO_2 into the reactor and heating at 150 °C for 5 h. Evacuation of oxygen from the reaction vessel prior to the admission of anhydrous CO_2 is suggested as a useful modification of Kolbe–Schmitt reaction conditions.

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