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Economical and Convenient Synthesis of *p*-Ethynylbenzoic Acid and *p*-Ethynylbenzoyl Chloride

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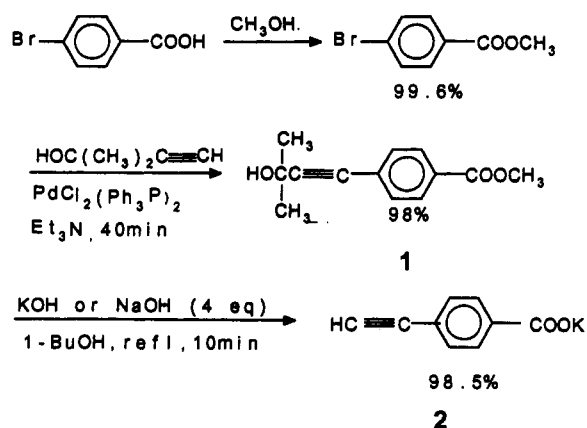
Five methods¹⁻⁸ have been reported for the synthesis of *m*- and *p*-ethynylbenzoic acids in yields varying from poor to moderate (26-59%). These methods require isolation and/or purification of intermediates and are cumbersome and costly to perform on a large scale.

The most important procedure for the synthesis of *p*-ethynylbenzoic acid (EBA) (and *p*-ethynylbenzoyl chloride (EBC) from EBA)⁵⁻⁸ involves coupling of methyl *p*-bromobenzoate with (trimethylsilyl)acetylene in the presence of palladium(0) complexes to give the (trimethylsilyl)ethynylated intermediate, followed by a two-step deprotection and hydrolysis. Because of the high cost of the (trimethylsilyl)acetylene, this method has been limited to laboratory preparations.

2-Methyl-3-butyn-2-ol (MEBYNOL) has been used by other investigators for synthesizing acetylene-terminated derivatives⁹⁻¹⁴ including ethynyl benzoic acid esters^{3,12} because of its very low cost. Sabourin and Onopchenko⁹ reported a convenient synthesis of 4-ethynylphthalic acid (anhydride) via MEBYNOL. Havens and Hergenrother¹² reported the synthesis of several arylacetylenes from 4-aryl-2-methyl-3-butyn-2-ols using sodium hydride as the base for deprotection. Shvartsberg and Moroz³ synthesized *o*-, *m*-, and *p*-ethynylbenzoic acid esters by deprotecting EtOCHMeOCMe₂CCC₆H₄CO₂Me in 27% total yield.

These methods^{1-8,12} have not been used for large-scale syntheses because the yields were low. Coupling of methyl *p*-bromobenzoate with (trimethylsilyl)acetylene⁵⁻⁸ and subsequent deprotection, although expensive,^{12,15} is the

Scheme I. Synthetic Route to *p*-Ethynylbenzoic Acid



present method of choice.¹⁶ Because of the high cost of (trimethylsilyl)acetylene, we decided to develop a high-yield synthetic route to EBA using the very cheap reagent, MEBYNOL.

Results and Discussion

A modified synthetic route to EBA and EBC was developed which is much cheaper and faster than previous methods and gives essentially quantitative yields (Scheme I). We took advantage of the sensitivity of the ester linkage toward potassium or sodium hydroxide to cleave the 2-hydroxypropyl group and saponify the ester simultaneously in 1-butanol or 2-propanol to prepare EBA in high yield.

Methyl *p*-bromobenzoate (MBB) was coupled with 2-methyl-3-butyn-2-ol (MEBYNOL) using Pd(0)/CuI catalysis to give the intermediate. 4-(4-(methoxycarbonyl)phenyl)-2-methyl-3-butyn-2-ol (1) in 98% yield with 99% purity. MBB was mixed with a small excess of MEBYNOL in deaerated, dried triethylamine/pyridine (volume ratio 5/2) in the presence of catalytic amounts of dichlorobis(triphenylphosphine)palladium, triphenylphosphine, and cuprous iodide, and the solution was refluxed. The reaction was complete in 40 min. The isolated intermediate was hydrolyzed and deprotected by refluxing in 1-butanol (10 min) or 2-propanol (2 h) using an excess of sodium or potassium hydroxide. The sodium or potassium salt of EBA precipitated quantitatively from the solution as it was formed (98.5% yield), with 99% purity.

EBA was obtained by acidifying an aqueous solution of the potassium or sodium salt to pH 2.5. It precipitated quantitatively as a white solid of 99% purity.

Crystalline EBA changes color from white to off-white on standing and then to light tan. Its GPC just after isolation shows a sharp single peak; the GPC of the off-white sample shows a slight broadening, which broadens more for the light tan sample. Based on the GPC changes, we postulate that EBA polymerizes slowly at room temperature. However, its sodium and potassium salts are stable.

The high yield in deprotection is probably obtained because while the dimethylethynylcarbinol salt is partially soluble in the alcohol, the deprotected salt precipitates quantitatively as it is formed. It is therefore protected against further attack by the base.

Ethynylbenzoyl chloride (EBC) was prepared in 99% yield and 99% purity by stirring either EBA or its salt with an excess of thionyl chloride in chloroform.

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The present method has several advantages over those of Takahashi,⁵ Austin,⁷ and Herbenrother^{8,15} because (1) MEBYNOL is used as a coupling agent instead of trimethylsilyl acetylene, (2) much higher overall yields of EBA and EBC are obtained, 97% instead of 59%¹⁵ and 96% instead of 39%,¹⁵ respectively, and (3) the overall reaction time was reduced from 14 h to 50 min.¹⁵

Experimental Section

General Methods. Melting points are uncorrected. Proton nuclear magnetic resonance (¹H-NMR) spectra were taken at 200 MHz. Chemical shifts (δ) are given in parts per million, with tetramethylsilane as internal standard. HPLC was run using a UV detector (254 nm) with methanol as the eluting solvent. GPC was run on a Waters GPC I equipped with a differential refractometer and a UV detector using two Plgel columns (5 μ m, 10 and 500 Å), with THF as the eluant.

Starting Materials. All reagents were used as received except pyridine and triethylamine which were refluxed over KOH pellets overnight and distilled just before use. Methyl *p*-bromobenzoate was prepared quantitatively by refluxing *p*-bromobenzoic acid (200 g) with an excess of methanol (400 g) and a catalytic amount of sulfuric acid (12 g) (purity: 99.7% by HPLC and GPC).

4-(4-(Methoxycarbonyl)phenyl)-2-methyl-3-butyn-2-ol (1). Dichlorobis(triphenylphosphine)palladium (0.48 g, 0.68 mmol) was added under N₂ to a solution of Ph₃P (1.74 g, 6.6 mmol), CuI (0.46 g, 2.4 mmol), methyl *p*-bromobenzoate (124.6 g, 580 mmol), and MEBYNOL (58 g, 690 mmol) in 800 mL of dry Et₃N and 320 mL of dry pyridine and refluxed under N₂ for 40 min. The mixture was cooled to rt and filtered to remove the insoluble triethylamine hydrobromide. The salt was washed with triethylamine and ethyl ether until the ether washings were clear. The combined filtrates were reduced to dryness under reduced pressure. The obtained solid was stirred twice with H₂O and then with 1 L of 3% HCl and again twice with H₂O. The mixture was filtered, and the residue was dried under vacuum to yield 1, light tan color (123.82 g, 98% yield), mp 84–85 °C (lit.¹² mp 83.5–84 °C, lit.³ mp 83.5–84 °C) and 99% purity (by HPLC and GPC). Compound 1 was recrystallized from a small volume of toluene to give off-white crystals (99.7% purity by HPLC and GPC).

***p*-Ethynylbenzoic Acid (2).** Sixty-six g (1.65 mol) of sodium hydroxide were dissolved in refluxing 1-butanol (2.6L); 90 g (0.41 mol) of 1 were added at once, and the mixture was refluxed for 10 min. After being cooled in an ice-bath and filtered, the white residue was stirred with refluxing 2-propanol (600 mL) twice and dried at 60 °C under vacuum to give the sodium salt of EBA (98.5% yield, 99% purity by analyzing the free acid by GPC). IR (KBr pellet, cm⁻¹): 3298 (C–H stretching of ethynyl); 2106 (weak band, C–C stretching of ethynyl); 1585 (asymmetric stretching of carboxylate anion); 1543 (C–C stretching of aromatic); 1390 (symmetric stretching of carboxylate anion); 621 (aromatic C–H deformation).

The hydrolysis-deprotection reaction was complete after 2 h at reflux using KOH (4 equiv), 5% w/v in 2-propanol.

p-Ethynylbenzoic acid was obtained by acidifying the salt solution to pH 2.5. It was obtained quantitatively as a white solid in 97% overall yield (lit.¹⁵ yield 59%) with 99% purity (by GPC) and mp 224–225 °C (lit.¹ mp 218 °C dec, lit.² mp 215–220 °C dec, lit.⁸ mp 222–223 °C dec, lit.¹⁵ mp 220–223 °C dec).

EBA salts are stable as solids and in solution. Upon acidification the acid precipitates; it changes color even at room temperature and while being dried under vacuum. Freshly synthesized, undried EBA can be stored without polymerization at –15 °C. It is noteworthy that the corresponding potassium or sodium salts are stable toward drying at 60 °C under vacuum and storage for extended periods at room temperature.

***p*-Ethynyl Benzoyl Chloride.** The potassium salt of EBA (94.0 g) in 300 mL of CHCl₃ was stirred at 0 °C, while SOCl₂ (140 mL) was added gradually. The reaction was exothermic. One mL of DMF was then added, and the mixture was stirred at rt for 5 h. The resulting orange solution was evaporated under vacuum to dryness at about 40 °C. The yellow residue was stirred sequentially with three 400-mL portions of ethyl ether for 30 min, and the combined filtrates were evaporated to dryness. A yellow crystalline product was obtained (83.3g), 99% yield, 96% overall

yield from methyl *p*-bromobenzoate (lit.¹⁵ yield 39%), mp 78–79 °C (lit.⁸ mp 68–69 °C, lit.¹⁵ mp 74.5–76 °C, lit.¹⁷ 76–77 °C and 99% purity (HPLC). ¹H-NMR (acetone-*d*₆): δ 8.12 (d, 2 H, *J* = 8.5 Hz, aromatic ortho to –COCl); 7.70 (d, 2 H, *J* = 8.5 Hz aromatic ortho to ethynyl group); 4.04 (s, 1 H, ethynyl group). FTIR (KBr pellet, cm⁻¹): 3267 (C–H stretching of ethynyl); 2106 (C–C stretching of ethynyl); 1776 (carbonyl stretching); 1730 (carbonyl stretching); 1689, 1588 (C–C stretching of aromatic ring); 1203 (C–H out of plane bending of aromatic ring). It should be noted that the absence of a band at 3550–3300 cm⁻¹ confirmed that EBC does not contain even traces of EBA. EBC was recrystallized from petroleum ether, hexanes, or a small volume of ethyl ether.

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Metalation-Alkylation of *O*-Trimethylsilyl Formyltrimethylsilane Cyanohydrin in the Synthesis of Oxazoles

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We have recently shown^{1,2} that *O*-trimethylsilyl acylsilane cyanohydrins 1 may be employed for the formation of oxazoles (Scheme I). Even though both acylsilanes (after TMSCN addition) and aldehydes (upon metalation-silylation of their *O*-trimethylsilyl cyanohydrins) have served as precursors to 1, the methodology would exhibit wider scope if 1 were accessible through R¹X alkylation of the carbanion derived from the metalation of 4 (Scheme II). Although 4 was readily available, our earlier observation³ that 4 could not be metalated by LDA seemed to preclude this approach. We now report that the less-hindered metal amides lithium dimethylamide and lithium diethylamide (LDEA) metalate 4 even at –95 °C.

To illustrate the utility of this approach, 4 was metalated with LDEA, followed by alkylation with a sampling of alkyl halides. The results (Table I) indicate that high yields of 1a–1e are obtained using either primary or secondary alkyl iodides (*tert*-butyl iodide gave no product⁴) or reactive alkyl bromides (benzyl chloride afforded a complex mixture of products). These species were then treated sequentially in the manner depicted by Scheme I to first afford 2a–2e⁵ which could then be converted without purification into the corresponding oxazoles 3a–3e in good overall yields (Table I). In particular, we note that this

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