Convenient syntheses of *m*- and *p*-ethynylphenols

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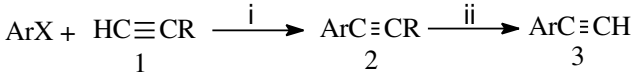
m-Iodophenol (**4a**) was found to couple with 2-methylbut-3-yn-2-ol (**5**) in the presence of $PdCl_2$–CuI–Ph_3P-in triethylamine to afford 3-(3-hydroxy-3-methylbut-1-ynyl)phenol (**6a**), which was conveniently converted into *m*-ethynylphenol (**7a**). Under the same conditions, *p*-iodophenol did not couple with **5**. However, *p*-iodo-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]benzene (**4b**) did react with **5** to afford 1-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-[2-hydroxy-2-methyl-4-but-3-ynyl]benzene (**6b**), which was similarly converted into 1-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-ethynylbenzene (**7b**) with loss of acetone. Removal of the tetrahydropyranyl protecting group from **7b** furnished *p*-ethynylphenol (**8**).

Keywords: ethynylphenol, synthesis, pyrolysis

Introduction

Reactive oligomers with a terminal acetylene moiety have great potential for high performance applications. They have high thermal stability and good mechanical properties under humid conditions.[1] *m*- and *p*-Ethynylphenol can be used as intermediates for fluorinated liquid crystals[2] and potential high temperature crosslinking endcapping agents for high transition temperature (T_g) arylene ethers. Some classical methods of synthesising arylacetylenes include the halogenation/dehydrohalogenation of ketones[3] or olefinic derivatives,[4] the displacement of halogens by cupric acetylides[5,6] and the reaction between the Vilsmeier reagent (DMF–$POCl_3$) and acetophenones.[7] These procedures are not reproducible enough[8] and the isolation and/or purification of the reaction products is cumbersome, costly, and unsafe to be performed on a preparative scale. In 1980, Songashira[9] described the palladium-catalyzed reaction of aryl halides with acetylenes (Scheme 1), which greatly facilitated the synthesis of arylalkynes.

According to Scheme 1, an aryl halide couples with a protected ethyne reagent **1** to afford the intermediate **2**, from which the target product **3** could be formed by a pyrolysis reaction. Trimethylsilylacetylene was a commonly used ethyne reagent in this procedure. However, due to the prohibitively high cost of trimethylsilylacetylene, this procedure is limited to laboratory preparations. Here we report a convenient procedure for the synthesis of *m*- and *p*-ethynylphenol (**7a** and **8**). Thus, 2-methylbut-3-yn-2-ol, which is inexpensive and commercially available, was used as the ethyne reagent instead of trimethylsilylacetylene. The hydroxyisopropyl group in the coupling products could be readily cleaved with loss of acetone. The synthetic pathway is outlined in Scheme 2.

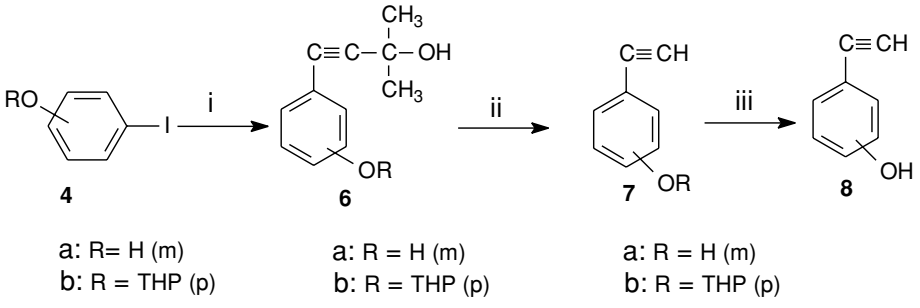


Scheme 1 Reagents and conditions: i, CuI, $(Ph_3P)_2PdCl_2$, Et_2NH, trimethylsilylacetylene, reflux; ii, potassium hydroxide, toluene, reflux.

Results and discussions

m-Iodophenol (**4a**) could directly couple with 2-methylbut-3-yn-2-ol (**5**) in the presence of $PdCl_2$–CuI–Ph_3P in triethylamine. Cleavage of the hydroxyisopropyl group in the coupling product (**6a**) was straightforward. However, *p*-iodophenol did not couple with **5** under the same conditions. It occurred to us that the hydroxyl group in *p*-iodophenol should be protected prior to the coupling reaction. We first acetylated the hydroxyl group of *p*-iodophenol (**4b**), and the resulting acetylated *p*-iodophenol did indeed couple with **5** to afford 1-acetoxy-4-[2-hydroxy-2-methyl-4-but-3-ynyl]benzene. The hydroxyisopropyl group in this compound could be readily removed with loss of acetone; but unblocking of the acetyl group was accompanied with some degree of polymerisation. It appeared that the acetyl group is more labile to base than the hydroxyisopropyl group and therefore concomitant loss of the acetyl group would occur under the conditions to remove the hydroxyisopropyl group. Furthermore, the acetyl group in 1-acetoxy-4-[2-hydroxy-2-methyl-4-but-3-ynyl]benzene could be removed in the presence of the hydroxyisopropyl group. However, cleavage of hydroxyisopropyl group could not be effected in the absence of the acetyl group. Therefore, a base-stable protecting group should be used to mask the hydroxyl group in *p*-iodophenol.

We then used 3,4-dihydro-2*H*-pyran (DHP) to protect the hydroxyl group of *p*-iodophenol. The protected compound



Scheme 2 Reagents and conditions: i, CuI, Ph_3P, $PdCl_2$, 2-methylbut-3-yn-2-ol, Et_3N, reflux; ii, potassium hydroxide, toluene, reflux; iii, pyridinium *p*-toluenesulfonate (PPTS), EtOH, 65 °C; THP ≡ tetrahydro-2*H*-pyran-yl.

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4b could couple with **5** to afford 1-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-[2-hydroxy-2-methyl-4-but-3-ynyl]benzene (**6b)** under the same conditions described above for **4a**. Removal of the hydroxyisopropyl group from **6b** was effected by heating **6b** with solid potassium hydroxide in toluene, thus furnishing 1-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-ethynyl-benzene (**7b**). Potassium hydroxide could be completely removed by filtration after the reaction was complete. Deprotection of the pyranyl protecting group from **7b** was performed in ethanol in the presence of pyridinium *p*-toluenesulfonate (PPTS) to give *p*-ethynyl phenol (**8**).

It was found that *p*-ethynylphenol **8** is more reactive than its *meta* isomer, and the former polymerises more readily, even at 60 °C. This pair of isomers also differs in their ^{1}H NMR spectra, where the hydroxyl proton in the *p*-isomer was not observed, presumably due to broadness.

For the coupling reaction between compounds **4** and **5**, it was found that the catalyst, *i.e.*, bis(triphenylphosphine) palladium(II) chloride, could be replaced with palladium(II) chloride and triphenylphosphine. However, the order of addition of the reagents was critical. Triphenylphosphine, copper(I) iodide and palladium(II) chloride should be mixed and stirred at 50 °C for 0.5 h before compound **4** is added.

Experimental

All the reagents and solvents were of commercial quality and were distilled or dried where necessary using the standard procedures. ^{1}H NMR spectra were recorded on a Bruker AVANCE 500 spectrometer operating at 500.13 MHz. Mass spectra were measured on an HP5989A mass spectrometer. Melting points were measured by X4 melting microscope apparatus (Beijing Analytic Instrument Factory). The thermometer was not corrected.

Synthesis of m-ethynylphenol (**7a**): To a 100 ml three-necked flask fitted with a condenser and a thermometer were added *m*-iodophenol **4a** (6.6 g, 0.030 mol), $PdCl_2$ (0.010 g, 0.056 mmol), CuI (0.020 g, 0.1 mmol), PPh_3 (0.060 g, 0.228 mmol) and triethylamine (40 cm^3). After the reaction mixture had been heated at 60 °C with stirring for 30 min, 2-methylbut-3-yn-2-ol **5** (2.94 g, 35 mmol) was added over a period of 5 min. The reactants were then heated at 80 °C for a further period of 3 h. The products were then cooled to room temperature, and filtered. The filtrate was concentrated under reduced pressure, and the residue was filtered through a short silica column, eluted with ethyl acetate–*n*-hexane (1:4 v/v). The appropriate fractions were combined and concentrated to dryness under reduced pressure to give **6a** as a white solid (4.54 g). The solid obtained was then taken up with toluene (50 cm^3) followed by addition of potassium hydroxide (50 mg, 0.89 mmol). The reactants were then heated under reflux for 3 h, during which time some solvent (*ca* 10 cm^3) was removed by distillation. Upon cooling, the products were neutralised with hydrochloride acid to *ca* pH 7 and then concentrated under reduced pressure. The residue was filtered through a short silica column, eluted with *n*-hexane–ethyl acetate (2:1 v/v). The appropriate fractions were pooled and concentrated under reduced pressure to give the *title compound* as a pale yellow oil (1.5 g, 43%). MS (EI, *m/e*): 118. δ_H [$CDCl_3$]: 3.07 (s, 1 H, -C≡H), 4.50–5.50 (broad, 1 H, –OH), 6.84 (d, 1 H, *J*= 7.9 Hz, Ar–H), 6.96 (s, 1 H, Ar–H), 7.07 (d, 1 H, *J*=7.7Hz, Ar–H), 7.19 (t, 1 H, *J*= 7.9Hz, *J*=7.9Hz, Ar–H) (lit[10]).

Synthesis of p-iodo-1-[(tetrahydro-2H-pyran-2-yl)oxy]benzene (**4b**): To a stirred solution of *p*-iodophenol (17.8 g, 81 mmol) and *p*-toluenesulfonic acid monohydrate (250 mg, 1.2 mmol) in dry dioxane (50 cm^3), 3,4-dihydro-2*H*-pyran (22 g, 252 mmol) was added dropwise over a period of 30 min while the temperature was maintained at 13–15 °C. After the reaction was complete as indicated by TLC (about 1 h), powdered $NaHCO_3$ (2 g) was added, and stirring was continued overnight. The products were then concentrated under reduced pressure. The residue was taken up with distilled water, and the precipitate was collected by filtration and dried to give a pale yellow solid. Recrystallisation of this solid from ethanol–water gave the *title compound* as white crystals (15.5 g, 65.3%). M.p. 57–59 °C. MS (EI, *m/e*): 304. δ_H [$CDCl_3$]: 1.55–2.05 (m, 6 H, –CH_2–), 3.55–3.85 (m, 2 H, –CH_2O–), 5.35 (t, *J* = 6.3 Hz, 1 H, –OCHO–), 6.81 (d, *J*= 8.8 Hz, 2 H, Ar–H), 7.53 (d, *J* =8.8 Hz, 2 H, Ar–H).*

Synthesis of 1-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[2-hydroxy-2-methyl-4-but-3- ynyl]benzene (**6b**): To a stirred solution of **4b** (15.5 g, 51 mmol) in dry triethylamine (60 cm^3) was added triphenylphosphine (0.076 g, 0.29 mmol), copper(I) iodide (0.020 g, 0.1 mmol) and palladium(II) chloride (0.024 g, 0.135 mmol). The mixture was then heated at 50 °C for 0.5 h. Compound **5** (5.6 g, 66 mmol) was then added quickly, and the reaction mixture was heated at 85 °C for 5 h. The products were then cooled to room temperature, and the precipitate was removed by filtration and the filter cake was washed with triethylamine (20 cm^3). The filtrate and washing liquor were combined and concentrated, and the residue was purified by column chromatography on silica gel. The appropriate fractions, which were eluted with ethyl acetate–*n*-hexane (1:4 v/v), were combined and concentrated under reduced pressure to give the *title compound* as an orange solid (12.4 g, 93%). M.p. 72–74 °C. MS (EI, *m/e*): 261. δ_H [$CDCl_3$]: 1.55–2.05(m, 6 H, –CH_2–), 1.60(s, 6 H, Me_2C–), 3.55–3.85 (m, 2 H, –CH_2O–), 5.39 (t, *J* =2.7 Hz, 1 H, –OCHO–), 6.90 (d, *J* =8.5 Hz, 2 H, Ar–H), 7.30 (d, *J*= 8.5 Hz, 2 H, Ar–H).*

Synthesis of 1-[(tetrahydro-2H-pyran-2-yl)oxy]-4-ethynyl benzene (**7b**): A solution of **6b** (17.5 g, 0.067 mmol) in dry toluene (250 cm^3) was stirred at 100 °C. To this solution was added powdered potassium hydroxide (6 g, 107.1 mmol). The mixture was maintained at this temperature for 6 h, while acetone-toluene was slowly distilled out. After the products were cooled to room temperature, the caustic residual particles were removed by filtration. The filtrate was concentrated under reduced pressure. The residue was dissolved in ether (200 cm^3), and washed with brine (100 cm^3) and distilled water (100 cm^3) respectively. The ether layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure to give compound **7b** as an orange solid (10.2 g, 75.4%). M.p. 64–66 °C. MS (EI, *m/e*): 202. δ_H [$CDCl_3$]: 1.55–2.05(m, 6 H, –CH_2–), 3.00 (s, 1 H, –C≡H), 3.55–3.85 (m, 2 H, –CH_2O–), 5.44 (t, *J* =6.4 Hz,1 H, –OCHO–), 6.98 (d, *J*= 8.7 Hz, 2H, Ar–H), 7.42 (d, *J*= 8.7 Hz, 2 H, Ar–H) (lit.[11]).

Synthesis of p-ethynylphenol (**8**): **7b** (10.2 g, 50.5 mmol) and PPTS (1.272 g, 5.36 mmol) were dissolved in dry ethanol (170 cm^3), and the solution was heated at 65 °C for 1 h. Upon cooling, the solvent was removed from the reaction products under reduced pressure and the residue was dissolved in aqueous NaOH (1 *M*, 300 cm^3). The aqueous solution was acidified with hydrochloric acid to weakly acidic pH, and then extracted with ether (3×100 cm^3). The organic layers were separated, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluted with *n*-hexane–ethyl acetate (5:1 v/v) . Evaporation of the appropriate fractions under reduced pressure gave the *title compound* as a pale yellow oil (4.0 g, 67%). MS (EI, *m/e*): 118. δ_H [$CDCl_3$]: 3.00 (s, 1 H, ≡C–H), 6.75 (d, *J*= 8.7 Hz, 2 H, Ar–H), 7.45(d, *J*= 8.7 Hz, 2 H, Ar–H) (lit[2]).

*Compounds **4b** and **6b** are novel. The structures are formally tentative but well supported by the spectroscopic evidence and their chemistry.

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