Electrochemically Induced $S_{RN}1$ Reactions: Selective Substitutions at 1,4-Dichlorobenzene

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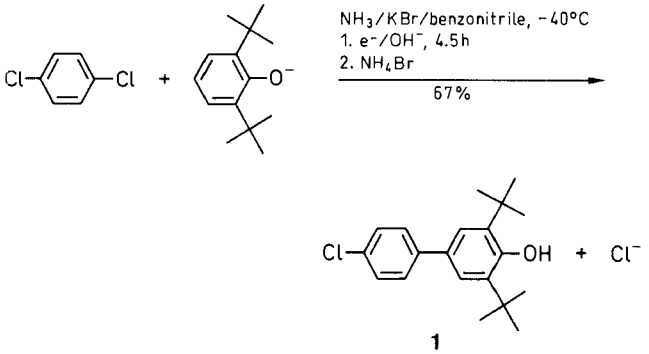
3',5'-Di-*tert*-butyl-4-chloro-4'-hydroxy-1,1'-biphenyl was obtained selectively by an electro-induced $S_{RN}1$ reaction, starting from 1,4-dichlorobenzene and 2,6-di-*tert*-butylphenoxide. The product was then further substituted to give a phosphine and (phosphoniophenyl)phenoxide zwitterions or carboxylated to obtain 3',5'-di-*tert*-butyl-4'-hydroxy-1,1'-biphenyl-4-carboxylic acid.

2,6-Di-*tert*-butylphenoxide (ArO^-) reacts with aromatic halides under $S_{RN}1$ conditions to give unsymmetrical biaryls.[1] These compounds are often regarded as precursors for liquid crystals or materials for non-linear optics.[2,3] The reaction yields are very high when the starting halide is substituted by an electron-withdrawing group such as CN, SO_2R, etc. Nonactivated aromatic halides are found to be nearly unreactive.[4]

Recently, Beugelmans et al. have shown that 4-bromofluorobenzene and ArO^- reacted by a photochemically stimulated $S_{RN}1$ reaction to give the fluorinated substitution product (yield: 30%). Under identical conditions, 1,4-diiodobenzene gave a mixture of reduction and monosubstitution products, with a total yield of 35%.[5] The two halogenated derivatives are interesting intermediates for a further substitution.

Here we describe the synthesis of 3',5'-di-*tert*-butyl-4-chloro-4'-hydroxy-1,1'-biphenyl **(1)** by an electrochemically induced $S_{RN}1$ reaction. We also give examples of subsequent substitution reactions: synthesis of a phosphine **2a**, phosphonio-phenoxide zwitterions **2c, 3b** and a carboxylic acid **4**.

Substitution of 1,4-dichlorobenzene by ArO^- was carried out by means of an electro-induced $S_{RN}1$ reaction in liquid ammonia:[6-8]



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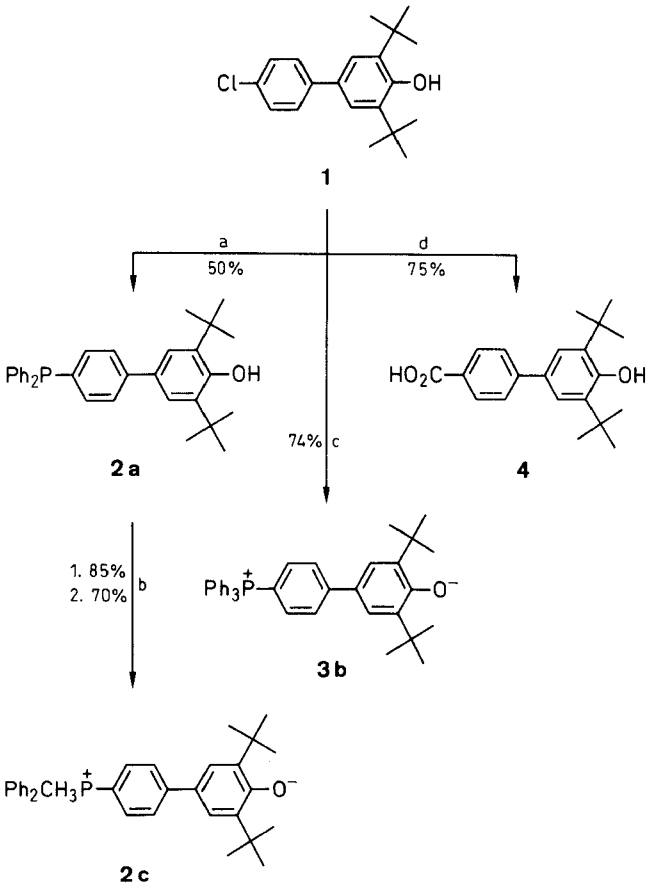
The reaction was induced by a redox mediator (benzonitrile). The classical use of a mediator under $S_{RN}1$ conditions is to impede the main competitive reaction, which is the reduction of the intermediate aryl radical (ClPh°). In the present case, since disubstitution competes with monosubstitution, the role of the mediator is also to oxidize the anion-radical of the monosubstitution product; the larger the concentration of the mediator, the more important monosubstitution over disubstitution.[9] In addition, since the solubility of 1,4-dichlorobenzene is small in liquid ammonia and large in benzonitrile, benzonitrile is also useful as a cosolvent to increase the solubility of the starting product in the reaction medium.

Further reactions of 3',5'-di-*tert*-butyl-4-chloro-4'-hydroxy-1,1'-biphenyl **(1)** are summarized in the following scheme:



(a) NH_3/KBr, −40°C; 1. PPh_2Cl/K; 2. e^-/OH^-/naphthalene 4 h; 3. NH_4Br. (b) 1. MeI/Et_2O, 25°C, 24 h; 2. NaOH/H_2O/CH_2Cl_2, 25°C. (c) 1. $PPh_3/NiCl_2$, 210°C, 5 h; 2. NaOH/H_2O. (d) DMF/$N(Bu)_4BF_4/CO_2$, 10°C, 2 h.

(a) Substitution of **1** by $P(Ph_2)^-$ was carried out again by means of an electro-induced $S_{RN}1$ reaction in liquid ammonia. The reaction was performed under similar conditions to those used for the preparation of **1**, except that (i) no cosolvent was needed, (ii) the nucleophile $P(Ph_2)^-$ had first to be prepared in situ by reduction of chlorodiphenylphosphine by potassium and (iii) naphthalene was used as a mediator.

(b) Quaternization of **2a** by methyl iodide was achieved in diethyl ether at room temperature, and followed by deprotonation to give zwitterion **2c**.

(c) Phosphine compounds are actually nucleophilic enough to react directly with aromatic halides at high temperatures.[10] Since chloride compounds are less reactive than the corresponding iodides or bromides, the reaction has to be performed with a catalyst (NiX_2, CoX_2, X: halide). When **1** was subjected to the reaction with triphenylphosphine/nickel(II) chloride, the obtained chloride salt **3a**, which was not isolated, was then deprotonated to give the corresponding zwitterion **3b**.

(d) Carboxylation of **1** was carried out by direct, non-mediated reduction in the presence of carbon dioxide under atmospheric pressure in dimethylformamide.[11-18]

In summary, monosubstitution product **1** could be synthesized selectively in good yield by a one-step reaction. The reaction can be extended to other aromatic dihalides (dichloropyridines) and other nucleophiles such as ethyl cyanoacetate. The results are to be published in another paper.[9] Some examples of a second substitution were given.

The potential interest of the two zwitterions **2c, 3b** for nonlinear optics was clearly demonstrated by their intense charge transfer band. The measurements of the hyperpolarizabilities in solution of these species are going on at present.

Carboxylic acid **4** could be an interesting subunit for liquid crystals after esterification by a long chain alcohol, di-*tert*-butylation and alkoxylation of the hydroxy group.

All the reagents were purchased from Aldrich and used without further purification. The electrochemical cells used with liquid NH_3 and DMF are described in Ref. 8 and Ref. 18 respectively. Melting points were measured with a hot stage microscope. ^1H, ^{13}C, ^{31}P NMR spectra were recorded on a Bruker spectrometer operating at 300 MHz, 75.5 MHz and 121.5 MHz, respectively. TMS was used as internal standard for ^1H and ^{13}C spectra; H_3PO_4 was used as external standard for ^{31}P spectra. Mass spectra were recorded on a Nermag R-10-10B instrument with electronic impact at 70 eV. UV spectra were recorded on a Kontron Uvikon 860 spectrophotometer. IR spectra were recorded on a Perkin-Elmer FTIR spectrophotometer. Combustion analyses were performed by the "Service de microanalse de l'Université Pierre et Marie Curie", Paris. Satisfactory microanalyses obtained for **1–4**: C ± 0.20, H ± 0.24; exceptions: **2b**: C − 0.70; **2c**: C − 1.20.

3′,5′-Di-*tert*-butyl-4-chloro-4′-hydroxy-1,1′-biphenyl (1):
Di-*tert*-butylphenol (10.63 g, 51.5 mmol), KOBu-*t* (8.93 g, 79.5 mmol) were successively introduced into a single-compartment electrochemical cell containing liquid NH_3 (200 mL) and KBr (6.2 g, 52 mmol) as supporting electrolyte. The temperature of the solution was maintained at −40 °C by a cryocooler. The excess of base (28 mmol) was neutralized by H_2O (700 mg, 39 mmol). To the suspension obtained, 1,4-dichlorobenzene (36 mmol, 5.3 g) which was first dissolved in benzonitrile (5.02 g, 36.5 mmol) was then added slowly. Such a process allowed the obtention of a finely divided suspension; 1,4-dichlorobenzene, which was nearly insoluble in liquid ammonia could then pass quickly into the solution when the electrolysis proceeded. The electrolysis was performed under galvanostatic conditions (i = 100 mA), using a stainless steel grid as the cathode (60 cm^2, 364 mesh cm^{-2}) and a sacrificial Mg rod as the anode. It was stopped when 1614 Coulombs (0.23 Faraday per mole of starting aromatic halide) had passed through the circuit. The solution was then neutralized by NH_4Br (10 g, 102 mmol). After NH_3 evaporation, the organic products were extracted by CH_2Cl_2 (2 × 250 mL). The solvent was evaporated. Benzonitrile and the unreacted phenol were distilled at 120 °C under partial vacuum (5–10 Torr). After cooling, the remaining solid was dissolved in the smallest volume of CH_2Cl_2. Product **1** was precipitated by addition of pentane. From the amounts of unreacted $PhCl_2$ (6 mmol, determined by HPLC) and Cl–Ph–ArOH (6.36 g, purity higher than 98 %), the reaction yield relative to the reacted starting aromatic dihalide could be estimated to about 67 %. Product **1** was recrystallized in hexane; mp 141 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.49 (s, 18 H), 5.28 (s, 1 phenolic H), 7.36 (s, 2 H), 7.40 and 7.46 (AA′BB′, J_{app} = 8 Hz, 4 H).

MS (CI, NH_3): m/z = 316 (M), 301, 300, 284, 283, 282, 267.

3′,5′-Di-*tert*-butyl-4-(diphenylphosphino)-4′-hydroxy-1,1′-biphenyl (2a):
PPh_2Cl (2.2 g, 10 mmol) and solid K (780 mg, 20 mmol) were introduced into a cell containing liquid NH_3 (80 mL, − 40 °C) and KBr (4 g, 34 mmol). The color of the solution turned to orange. Product **1** (316 mg, 1 mmol), H_2O (1 mmol, 18 mg), KOBu-*t* (112 mg, 1 mmol) and naphthalene (mediator, 128 mg, 1 mmol) were successively introduced into the cell. A constant current intensity of 20 mA was imposed between a platinum grid (8 cm^2, 1024 mesh cm^{-2}) and a Mg rod for 4 h. The reaction was monitored by cyclic voltammetry and stopped when the reduction peak of **1** had disappeared. The solution was then neutralized by NH_4Br (5.88 g, 60 mmol). After evaporation of NH_3, the organic products were extracted by CH_2Cl_2. They were separated by flash chromatography (silica gel, pentane/CH_2Cl_2, 70:30). The yield of isolated product **2a** was 50 % (650 mg). The main secondary product was the reduction product ArNu. Product **2a** was recrystallized in MeCN; mp = 143 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 18 H), 5.30 (1 phenolic H), 7.30 (s, 2 H), 7.35 to 7.55 (m, 14 H).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = − 8.1 (m, 1 P).

MS (EI): m/z = 467 (M + 1), 466.

MS (CI, NH_3): m/z = 483 (M + 17), 467, 183.

UV (CH_2Cl_2): λ_{1max} = 291 nm, ε_{1max} = 26000, λ_{2max} = 228 nm, ε_{2max} = 25000.

3′,5′-Di-*tert*-butyl-4-(methyldiphenylphosphonio)-4′-hydroxy-1,1′-biphenyl Iodide (2b):
Quaternization of **2a** by MeI was achieved at r.t. by stirring **2a** (154 mg, 0.33 mmol) and CH_3I (568 mg, 4 mmol) in anhydr. Et_2O (30 mL) for 24 h. The yield of isolated product **2b** was 85 % (170 mg); mp > 300 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 18 H), 3.23 (d, 3 H, J_{HP} = 14 Hz), 5.47 (s, 1 phenolic H), 7.43 (s, 2 H, 7.66–7.89 (m, 14 H).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 19.6 (m, 1 P).

MS (EI): m/z = 482 (M + 1), 481, 466, 451, 410, 204, 142, 143, 128, 127, 120, 104.

UV (CH_2Cl_2): λ_{max} = 217 nm, ε_{max} = 25000.

IR (KBr pellet): ν_{CP} = 906 cm^{-1}.

1,3-Di-*tert*-butyl-4-[4-(methyldiphenylphosphonio)phenyl]phenoxide (2c): Compound **2b** (220 mg, 0.457 mmol) was dissolved in CH_2Cl_2 (50 mL) and added to a molar solution of NaOH (20 mL). The organic phase was then separated and the operation was repeated twice. The orange organic phase was then filtered over phase separator paper and concentrated. The product was precipitated by addition of Et_2O and dried at 100 °C under partial vacuum for 5 h. The yield of isolated product **2c** was 70 % (153 mg). The product **2c** was recrystallized in $CHCl_3$; color: orange-red; mp > 300 °C.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.35 (s, 18 H), 3.02 (d, 3 H, J_{HP} = 14 Hz), 7.21 (s, 2 H), 7.58–7.88 (m, 14 H).

^{31}P NMR (121.5 MHz, CD_3OD): δ = 22.7 (m).

MS (EI): m/z = 481 (M + 1), 466, 142, 127.

UV (CH_2Cl_2): λ_{max} = 480 nm, ε_{max} = 45000.

IR (KBr pellet): ν_{CP} = 902 cm^{-1}.

1,3-Di-*tert*-butyl-4-[4-(triphenylphosphonio)phenyl]phenoxide (3b):
The molten mixture of $NiCl_2$ (130 mg, 1 mmol), **1** (1.26 g, 4 mmol) and PPh_3 (524 mg, 2 mmol) was stirred for 5 h at 210 °C. After

cooling, H_2O was first added to the mixture, then NaOH. Product **2** was extracted by CH_2Cl_2 and dried ($MgSO_4$). It was concentrated, precipitated by addition of cyclohexane and recrystallized in $CHCl_3$. The yield of isolated product **2** relative to PPh_3 was 74% (815 mg); color: red; mp > 300 °C.

^{1}H NMR (90 MHz, acetone): δ = 1.5 (s, 18 H), 7.5–8.1 (m, 21 H).
^{31}P NMR (121.5 MHz, CD_3OD): δ = 24.4 (m, 1 P).
UV (CH_2Cl_2): λ_{max} = 498 nm, ε_{max} = 41000.

3',5'-Di-*tert*-butyl-4'-hydroxy-1,1'-biphenyl-4-carboxylic Acid (4): Compound **1** (1 g, 3.16 mmol) was introduced into a single-compartment electrochemical cell containing DMF (30 mL) freshly distilled over CaH_2 and $Bu_4N^+BF_4^-$ (0.5 g, 1.5 mmol) (supporting electrolyte). CO_2 was supplied under atmospheric pressure. The temperature of the cell was maintained at 10 °C. A constant intensity of 200 mA was imposed between a 20 cm^2 stainless steel grid (364 mesh cm^{-2}) and a Mg rod as the anode. The experiment was stopped when 1500 Coulombs (5 F per mole of **1**) had passed through the circuit. After evaporation of DMF and acidic hydrolysis with aq HCl till pH = 1, product **4** was extracted three times by CH_2Cl_2 (200 mL). The product was obtained by flash chromatography over silica gel (pentane/Et_2O, 90:10 then Et_2O). It was dissolved in the minimum of Et_2O and precipitated in pentane. The conversion yield was 90%. The yield of isolated product **4** relative to the reacted starting product **1** was 75% (773 mg); mp 255 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.5 (s, 18 H), 5.3 (s, 1 phenolic H), 7.3 (s, 2 H), 7.6 and 8.1 (AA'BB', J_{app} = 9 Hz, 4 H), 9.5–10.5 (br s, 1 carboxylic H).
MS (CI, NH_3): m/z = 327 (M + 1), 326, 311.

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