Synthesis of diphenyl(X)phosphonium betaines (X = CH₃, C₆H₅, 2,5-F₂C₆H₃) from hexafluoro-1,4-naphthoquinone

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Dedicated to Professor Usein M Dzhemilev on the occasion of his 65th birthday

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Abstract
Betaines 5,6,7,8-tetrafluoro-3-(triphenyl-λ⁵-phosphanylidene)-1,2,3,4-tetrahydronaphthalene-1,2,4-trione, 5,6,7,8-tetrafluoro-3-(methylidiphenyl-λ⁵-phosphanylidene)-1,2,3,4-tetrahydronaphthalene-1,2,4-trione, and 3-[(2,5-difluorophenyl)diphenyl-λ⁵-phosphanylidene]-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydronaphthalene-1,2,4-trione have been synthesized via fluorine substitution in the quinone ring of hexafluoro-1,4-naphthoquinone by tertiary phosphines RPh₂P (R = Me, Ph, 2,5-F₂C₆H₃) and methanol in 90, 30 and 62% yields, respectively. The first naphthalenetriene formed also upon interaction of pentafluoro-1,4-naphthoquinone with triphenylphosphine in methanol. The new 1,4-dibenzodioxine derivative – 6,11-difluoro-9-(triphenyl-λ⁵-phosphanylidene)-7,8,9,10-tetrahydro-5,12-dioxatetracene-7,8,10-trione – has been obtained in a 83% yield by fluorine substitution in the benzene moiety of a naphthoquinone skeleton of this betaine by the action of pyrocatechol at the presence of potassium carbonate in DMSO.

Keywords: Tertiary phosphines, polyfluorinated 1,4-naphthoquinones, phosphonodiodefluorination, phosphonium betaines, 5,12-dioxatetracene.

Introduction

Amino derivatives of polyfluorinated 1,4-naphthoquinones are potential inhibitors of tumoral cells growth and antioxidants protecting cells against spontaneous mutagenesis. Among them there is an ammonium betaine – 1,4-dioxo-3-(1-pyridinio)-1,4-dihydro-5,6,7,8-tetrafluoronaphthalene-2-olate I, obtained by fluorine substitution in the quinone ring of
hexafluoro-1,4-naphthoquinone 2 by action of pyridine and methanol.\(^1\) The phosphonium analogues of ammonium betaine are also of interest for studying their biochemical properties. It was noted that the reaction of 2,3-dichloro-1,4-naphthoquinone with triphenylphosphine in methanol gave a phosphonium betaine – 3-(triphenylphosphorylidene)-1,2,4(3H)-naphthalenetrione in a 68% yield.\(^2,3\)

![Chemical structures](image)

In this connection, in the present work we report the synthesis of 5,6,7,8-tetrafluoro-1,4-naphthoquinone phosphonium betaines via phosphoniodefluorination of quinone 2 and 2,5,6,7,8-pentafluoro-1,4-naphthoquinone 3 by the action of phosphines RPh\(_2\)P (R = Me, Ph, 2,4-F\(_2\)C\(_6\)H\(_3\)) and methanol. The possibility to modify betaines of this type via fluorine nucleophilic substitution in the benzene ring of a naphthaquionone skeleton is exemplified by heterocyclization to construct a benzodioxin core.

**Results and Discussion**

**Synthesis of phosphonium betaine derivatives of 5,6,7,8-tetrafluoro-1,4-naphthoquinone**

Interaction of quinone 2 with triphenylphosphine in methanol gave in a 90% yield a betaine – 5,6,7,8-tetrafluoro-3-(triphenyl-λ\(_5\)-phosphanylidene)-1,2,3,4-tetrahydronaphthalene-1,2,4-trione 4 – whose electronic structure could be depicted in a first approximation by a resonance of structures C, D, and E (Scheme 1).

![Reaction scheme](image)

**Scheme 1.** General synthetic route to the title compounds 4–6.
Analogously to the earlier described synthesis of ammonium betaine 1, one may believe that phosphonium salt A is originally formed, in which a triphenylphosphonium group activates effectively the neighboring position 3 for a nucleophilic attack, whereupon the rapid F\textsuperscript{3} substitution occurs by methanol to give quinone B. Nucleophilic demethylation of this quinone by the action of a fluoride anion leads to 4. Similarly, by the action of diphenyl(2,5-difluorophenyl)phosphine or biphenylmethylphosphine on quinone 2 synthesized are, respectively. 3-[(2,5-difluorophenyl)diphenyl-\(\lambda^5\)-phosphanylidene]-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydronaphthalene-1,2,4-trione 5 or 5,6,7,8-tetrafluoro-3-(methyldiphenyl-\(\lambda^5\)-phosphanylidene)-1,2,3,4-tetrahydronaphthalene-1,2,4-trione 6 (Scheme 1).

The interaction of naphthoquinone 3 with triphenylphosphine resulted in \(\sim\)25% consumption of the starting material to give betaine 4 in 18% isolated yield (Scheme 2).

\textbf{Scheme 2.} Formation of betaine 4 from quinone 3.

By analogy to Scheme 1 and literature data, this transformation consists supposedly in formation of phosphonium salt F and the subsequent methanol addition to its position 3 to give betaine G. The latter adds HF to give hydroquinone H, which is oxidized, apparently, by quinones being present in the system to compound B that converts eventually to betaine 4.

**Aryloxydefluorination of quinone 2 by action of pyrocatechol**

Compounds 4–6 are promising building blocks for the synthesis of various derivatives as potentially biologically active compounds. Ample opportunities of their modification on a
benzene moiety are afforded by use of fluorine nucleophilic substitutions. In the present work this is exemplified by the equimolar interaction of 4 with pyrocatechol in the presence of potassium carbonate to yield a 1,4-dibenzodioxin derivative – 6,11-difluoro-9-(triphenyl-λ^5-phosphanylidene)-7,8,9,10-tetrahydro-5,12-dioxatetracene-7,8,10-trione 7 (Scheme 3).

![Scheme 3. Synthesis of 5,12-dioxatetracene 7.](image)

Its structure is confirmed by the presence in the ^19_F NMR spectrum of two doublets with \( \text{para}_{J_{FF}} = 13.6 \text{ Hz} \) belonging to F^6 and F^11. Two isomers of 7 were also observed in the product mixture in amounts of 4 to 10% emerging obviously via substitution of F^5 and F^6 or F^7 and F^8 in 4. They manifest themselves by the presence of doublets with \( \text{ortho}_{J_{FF}} = 19–20 \text{ Hz} \) in a ^19_F NMR spectrum.

All new compounds were characterized by ^1_H, ^19_F, and ^31_P NMR spectra and MS data (see the experimental section). The ^19_F NMR characteristics of quinones 4–6 nicely agree with similar data for pyridinium betaine: 4 signals in these spectra are multiplets located at \( \delta = 22–24 \) for F^5 and F^6 and 11–17 ppm for F^6 and F^7, their spin coupling structures being typical for ortho disubstituted tetrafluorobenzenes (\( \text{ortho}_{J_{FF}} \approx 19, \text{meta}_{J_{FF}} = 8–10, \text{para}_{J_{FF}} = 13.6–13.8 \text{ Hz} \)).

**Experimental Section**

**General.** ^1_H NMR, ^19_F, and ^31_P spectra were recorded on a Bruker AV-300 spectrometer [300.13, 282.36, and 121.50 MHz, respectively] with residual protons in deuterated solvents, external C\(_6\)F\(_6\) and internal H\(_3\)PO\(_4\) as standards. HRMS data were obtained with a “DFS” spectrometer. The melting points were determined on an FP 900 Thermosystem microscope melting point apparatus (Mettler-Toledo International Inc., Zürich, Switzerland). Solvents and reagents were reagent quality.

Compounds 2,^6^3^7^ and diphenyl(2,5-difluorophenyl)phosphine^8^ were prepared according to the literature procedures. Methanol and methylene chloride were distilled. DMSO was dried by molecular sieves 3Å. Triphenylphosphine was crystallized from diethyl ether.
5,6,7,8-Tetrafluoro-3-(triphenyl-\(\lambda^5\)-phosphanylidene)-1,2,3,4-tetrahydronaphthalene-1,2,4-trione (4). Method A. A mixture of quinone 2 (0.048 g, 0.180 mmol), triphenylphosphine (0.049 g, 0.187 mmol) and methanol (0.75 mL) was stirred under argon for 48 h at 20 °C. A precipitate was centrifuged off, washed with methanol (2×0.5 mL), dried in vacuum (0.5 torr) to obtain compound 4 (0.048 g, 53%). After evaporation of the solvent, the dry residue was crystallized from ethanol to yield an additional amount (0.034 g) of the product, an overall yield of 4 being 0.082 g (90%), bright yellow crystals thermally decomposing without melting. \(^1\)H NMR ((CD\(_3\))\(_2\)CO), \(\delta\) 7.8 (m, 6H, CH), 7.7 (m, 3H, CH), 7.6 (m, 6H, CH). \(^{19}\)F NMR ((CD\(_3\))\(_2\)CO), \(\delta\) 22.4 (ddd, \(\text{ortho}\) \(J\)\(_{\text{FF}}\) \(\approx\) 19 Hz, \(\text{meta}\) \(J\)\(_{\text{FF}}\) \(\approx\) 10 Hz, \(\text{para}\) \(J\)\(_{\text{FF}}\) = 13.8 Hz, F\(^5\) or \(8\)), 21.8 (ddd, \(\text{ortho}\) \(J\)\(_{\text{FF}}\) \(\approx\) 19 Hz, \(\text{meta}\) \(J\)\(_{\text{FF}}\) \(\approx\) 8 Hz, \(\text{para}\) \(J\)\(_{\text{FF}}\) = 13.8 Hz, F\(^5\) or \(8\)), 15.9 (ddd, \(\text{ortho}\) \(J\)\(_{\text{FF}}\) \(\approx\) 19 Hz, \(\text{meta}\) \(J\)\(_{\text{FF}}\) \(\approx\) 10 Hz, F\(^6\) or \(7\)), 11.0 (ddd, \(\text{ortho}\) \(J\)\(_{\text{FF}}\) \(\approx\) 19 Hz, \(\text{meta}\) \(J\)\(_{\text{FF}}\) \(\approx\) 8 Hz, F\(^6\) or \(7\)). \(^{31}\)P\(^{1}\)H NMR ((CD\(_3\))\(_2\)CO), \(\delta\) 15.3 (s). MS, \(m/z\) \((I_{\text{rel}}, \%)\): 506 [M\(^+\)] (14), 477 [M–H–CO\(^+\)] (48), 262 [M–C\(_{10}\)F\(_4\)O\(_3\)]\(^+\) (100). HRMS for C\(_{28}\)F\(_4\)H\(_{15}\)O\(_3\)P [M\(^+\)]; calcd. 506.0690, found 506.0685.

Method B. A mixture of quinone 3 (0.0925 g, 0.373 mmol), triphenylphosphine (0.0978 g, 0.373 mmol) and methanol (1.5 mL) was stirred for 2 weeks under argon at 20 °C and analyzed by \(^{19}\)F NMR and \(^{31}\)P NMR (Scheme 2). Methanol was distilled off up to a residual volume of 0.5 mL, a precipitate was centrifuged off and purified by TLC (Sorbfil, diethyl ether) to yield compound 4 (0.033 g, 18%).

3-[(2,5-Difluorophenyl)diphenyl-\(\lambda^5\)-phosphanylidene]-5,6,7,8-tetrafluoro-1,2,4-trione (5). A mixture of quinone 2 (0.076 g, 0.285 mmol), diphenyl(2,5-difluorophenyl)phosphine (0.085 g, 0.285 mmol) and methanol (1.3 mL) was stirred for 48 h under argon at 20 °C. A precipitate was centrifuged off, washed with methanol (2×0.2 mL) and dried in vacuum (0.5 torr) to give the title compound 5 (0.096 g, 62%) as bright yellow crystals thermally decomposing without melting. \(^1\)H NMR ((CD\(_3\))\(_2\)CO, CH\(_2\)Cl\(_2\)), \(\delta\) 7.92–7.81 (m, 4H, C\(_6\)H\(_5\)), 7.80–7.71 (m, 2H, C\(_6\)H\(_5\)), 7.69–7.58 (m, 4H, C\(_6\)H\(_5\)), 7.51 (m, 1H, C\(_6\)F\(_2\)H\(_3\)), 7.29 (m, 1H, C\(_6\)F\(_2\)H\(_3\)), 7.05 (m, 1H, C\(_6\)F\(_2\)H\(_3\)). \(^{19}\)F NMR ((CD\(_3\))\(_2\)CO, CH\(_2\)Cl\(_2\)), \(\delta\) 61.8 (m, 1F, C\(_6\)F\(_2\)H\(_3\)), 46.7 (m, 1F, C\(_6\)F\(_2\)H\(_3\)), 23.6 (ddd, \(\text{ortho}\) \(J\)\(_{\text{FF}}\) \(\approx\) 19 Hz, \(\text{meta}\) \(J\)\(_{\text{FF}}\) \(\approx\) 10 Hz, \(\text{para}\) \(J\)\(_{\text{FF}}\) = 13.8 Hz, F\(^5\) or \(8\)), 22.7 (ddd, \(\text{ortho}\) \(J\)\(_{\text{FF}}\) \(\approx\) 19 Hz, \(\text{meta}\) \(J\)\(_{\text{FF}}\) \(\approx\) 9 Hz, \(\text{para}\) \(J\)\(_{\text{FF}}\) = 13.8 Hz, F\(^5\) or \(8\)), 17.1 (ddd, \(\text{ortho}\) \(J\)\(_{\text{FF}}\) \(\approx\) 19 Hz, \(\text{meta}\) \(J\)\(_{\text{FF}}\) \(\approx\) 10 Hz, F\(^6\) or \(7\)), 12.5 (ddd, \(\text{ortho}\) \(J\)\(_{\text{FF}}\) \(\approx\) 19 Hz, \(\text{meta}\) \(J\)\(_{\text{FF}}\) \(\approx\) 9 Hz, F\(^6\) or \(7\)). \(^{31}\)P\(^{1}\)H NMR ((CD\(_3\))\(_2\)CO, CH\(_2\)Cl\(_2\)), \(\delta\) 9.4 (dd, \(\text{\(^2\)J}\)\(_{\text{PF}}\) \(\approx\) 4 \(\text{\(^2\)J}\)\(_{\text{PF}}\) = 3 Hz). MS, \(m/z\) \((I_{\text{rel}}, \%)\): 542 [M\(^+\)] (7), 513 [M–H–CO\(^+\)] (28), 298 [M–C\(_{10}\)F\(_4\)O\(_3\)]\(^+\) (100). HRMS for C\(_{28}\)F\(_4\)H\(_{15}\)O\(_3\)P [M\(^+\)]; calcd. 542.0501, found 542.0490.

5,6,7,8-Tetrafluoro-3-(methylidiphenyl-\(\lambda^5\)-phosphanylidene)-1,2,3,4-tetrahydronaphthalene-1,2,4-trione (6). A mixture of quinone 2 (0.100 g, 0.376 mmol), diphenylmethylphosphine (0.075 g, 0.376 mmol) and methanol (1.5 mL) was stirred for 48 h under argon at 20 °C to give the mixture containing compounds 6 and 2 (64 and 18%, accordingly). The solvent was distilled off, a residue was crystallized from ethanol (1 mL) and purified by TLC (Sorbfil, chloroform) to yield the title compound 6 (0.05 g, 30%), bright yellow crystals, mp 179 °C. \(^1\)H NMR ((CD\(_3\))\(_2\)CO), \(\delta\) 7.92–7.81 (m, 4H, C\(_6\)H\(_5\)), 7.76–7.68 (m, 2H, C\(_6\)H\(_5\)), 7.66–7.58 (m, 4H, C\(_6\)H\(_5\)), 2.6 (d, \(\text{\(^2\)J}\)\(_{\text{PH}}\) = 14.2 Hz, 3H, CH\(_3\)). \(^{19}\)F NMR ((CD\(_3\))\(_2\)CO), \(\delta\) 22.5 (ddd, \(\text{ortho}\) \(J\)\(_{\text{FF}}\) \(\approx\) 19 Hz, \(\text{meta}\) \(J\)\(_{\text{FF}}\) \(\approx\) 10 Hz, \(\text{para}\) \(J\)\(_{\text{FF}}\) \(\approx\) 10 Hz).
Hz, $\text{para}_{\text{FF}} = 13.8$ Hz, $F^5_{\text{or} 8}$), 21.8 (ddd, $\text{ortho}_{\text{FF}} \approx 19$ Hz, $\text{meta}_{\text{FF}} \approx 8$ Hz, $\text{para}_{\text{FF}} = 13.8$ Hz, $F^5_{\text{or} 8}$), 15.9 (ddd, $\text{ortho}_{\text{FF}} \approx 19$ Hz, $\text{meta}_{\text{FF}} \approx 10$ Hz, $F^6_{\text{or} 7}$), 11.1 (ddd, $\text{ortho}_{\text{FF}} \approx 19$ Hz, $\text{meta}_{\text{FF}} \approx 8$ Hz, $F^6_{\text{or} 7}$). $^{31}$P$^1$H NMR ((CD$_3$)$_2$CO), $\delta$ 13.6 (s). MS, $m/z$ ($I_{rel}$, %): 444 [M$^+$] (6), 200 [M–C$_{10}$F$_3$O$_3$]$^+$ (62). HRMS for C$_{23}$F$_4$H$_{13}$O$_3$P [M$^+$]: calcd. 444.0533, found 444.0535.

6,11-Difluoro-9-(triphenyl-$\lambda^5$-phosphanylidene)-7,8,9,10-tetrahydro-5,12-dioxtetracene-7,8,10-trione (7). A mixture of betaine 4 (0.051 g, 0.101 mmol), pyrocatechol (0.011 g, 0.101 mmol), potassium carbonate (0.028 g, 0.203 mmol) and DMSO (1.5 mL) was stirred for 6 h at 20 °C and analyzed by $^{19}$F and $^{31}$P NMR (Scheme 3). Water (3 mL) was added, a precipitate was centrifuged off, washed with water (1 mL), dried on air and the titled compound 7 (0.048 g, 83%) was isolated by TLC (Sorbfil, chloroform–methylene chloride, 1:1) as bright yellow crystals decomposing at heating without melting. $^1$H NMR (CDCl$_3$), $\delta$ 7.73–7.64 (m, 3H, C$_6$H$_3$), 7.64–7.56 (m, 3H, C$_6$H$_3$), 7.02–6.97 (m, 4H, C$_6$H$_4$). $^{19}$F NMR (CDCl$_3$), $\delta$ 24.0 (d, $\text{para}_{\text{FF}} = 13.6$ Hz, $F^6_{\text{or} 11}$), 21.6 (d, $\text{para}_{\text{FF}} = 13.6$ Hz, $F^6_{\text{or} 11}$). $^{31}$P$^1$H NMR (CDCl$_3$), $\delta$ 14.8 (s). MS, $m/z$ ($I_{rel}$, %): 577 [M+H]$^+$ (2), 547 [M–H–CO]$^+$ (25), 262 [M–C$_{16}$H$_8$F$_2$Os]$^+$ (52). HRMS for C$_{34}$F$_7$H$_{16}$O$_3$P [M+H]$^+$: calcd. 577.1011, found [M+H]$^+$ 577.1310.

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