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

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 naphthalenetrione 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, phosphoniodefluorination, 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.¹ 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.\textsuperscript{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-(triphenylphosphoranylidene)-1,2,4(3\textit{H})-naphthalenetricrone in a 68% yield.\textsuperscript{2,3}

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\textsubscript{2}P (R = Me, Ph, 2,4-F\textsubscript{2}C\textsubscript{6}H\textsubscript{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-\textlambda\textdegree-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).

![Scheme 1](https://example.com/scheme1.png)

**Scheme 1.** General synthetic route to the title compounds 4–6.
Analogously to the earlier described synthesis of ammonium betaine \(1^4\), 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 \(F^3\) 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 \(~25\%\) consumption of the starting material to give betaine \(4\) in 18\% isolated yield (Scheme 2).

**Scheme 2.** Formation of betaine \(4\) from quinone \(3\).

By analogy to Scheme 1 and literature data,\(^5\) 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 \(4\).

**Aryl oxy defluorination 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-λ³-phosphanylidene)-7,8,9,10-tetrahydro-5,12-dioxatetracene-7,8,10-trione 7 (Scheme 3).

\[
\text{4} + \text{HO} \quad \text{K}_2\text{CO}_3 \quad \text{DMSO, 20}^\circ\text{C} \quad \text{7}
\]

\[
\text{83%}
\]

**Scheme 3.** Synthesis of 5,12-dioxatetracene 7.

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

All new compounds were characterized by \(^1\text{H},\, ^{19}\text{F},\) and \(^{31}\text{P}\) NMR spectra and MS data (see the experimental section). The \(^{19}\text{F}\) 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 \(\text{F}^5\) and \(\text{F}^6\) and 11–17 ppm for \(\text{F}^6\) and \(\text{F}^7\), their spin coupling structures being typical for \(\text{ortho}\) disubstituted tetrafluorobenzenes (\(\text{ortho}\, J_{\text{FF}} \approx 19,\, \text{meta}\, J_{\text{FF}} = 8–10,\, \text{para}\, J_{\text{FF}} = 13.6–13.8\) Hz).

**Experimental Section**

**General.** \(^1\text{H}\) NMR, \(^{19}\text{F},\) and \(^{31}\text{P}\) 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 \(\text{C}_6\text{F}_6\) and internal \(\text{H}_3\text{PO}_4\) 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., Zurich, Switzerland). Solvents and reagents were reagent quality.

Compounds 2, 6, 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 give the title compound 4 (0.048 g, 0.187 mmol) as 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, ortho\(J_{\text{FF}}\) ≈ 19 Hz, meta\(J_{\text{FF}}\) ≈ 10 Hz, para\(J_{\text{FF}}\) = 13.8 Hz, F\(^5\) or \(^8\)), 15.9 (ddd, ortho\(J_{\text{FF}}\) ≈ 19 Hz, meta\(J_{\text{FF}}\) ≈ 10 Hz, F\(^6\) or \(^7\)), 11.0 (ddd, ortho\(J_{\text{FF}}\) ≈ 19 Hz, meta\(J_{\text{FF}}\) ≈ 8 Hz, F\(^6\) or \(^7\)). \(^31\)P\(^{\text{1H}}\) 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\(_{3}\)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-tetrahydronaphthalene-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\(_5\)). 19F 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, ortho\(J_{\text{FF}}\) ≈ 19 Hz, meta\(J_{\text{FF}}\) ≈ 10 Hz, para\(J_{\text{FF}}\) = 13.8 Hz, F\(^5\) or \(^8\)), 22.7 (ddd, ortho\(J_{\text{FF}}\) ≈ 19 Hz, meta\(J_{\text{FF}}\) ≈ 9 Hz, para\(J_{\text{FF}}\) = 13.8 Hz, F\(^5\) or \(^8\)), 17.1 (ddd, ortho\(J_{\text{FF}}\) ≈ 19 Hz, meta\(J_{\text{FF}}\) ≈ 10 Hz, meta\(J_{\text{FF}}\) ≈ 9 Hz, F\(^5\) or \(^8\)). \(^31\)P\(^{\text{1H}}\) NMR ((CD\(_3\))\(_2\)CO, CH\(_2\)Cl\(_2\)), \(\delta\) 3.9–4 (ddd, ortho\(J_{\text{FF}}\) ~ 4 Hz = 3 Hz). MS, \(m/z\) (\(I_{\text{rel}}\), %): 513 [M\(^+\) (7), 513 [M–H–CO]\(^+\) (28), 298 [M–C\(_{10}\)F\(_4\)O\(_3\)]\(^+\) (100). HRMS for C\(_{28}\)F\(_{3}\)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, \(J_{\text{PH}}\) = 14.2 Hz, 3H, CH\(_3\)). \(^19\)F NMR ((CD\(_3\))\(_2\)CO), \(\delta\) 22.5 (ddd, ortho\(J_{\text{FF}}\) ≈ 19 Hz, meta\(J_{\text{FF}}\) ≈ 10 Hz, F\(^5\) or \(^8\)).
Hz, \( \text{para} J_{\text{FF}} = 13.8 \text{ Hz}, F^5 \text{ or } 8 \), 21.8 (ddd, \( \text{ortho} J_{\text{FF}} \approx 19 \text{ Hz}, \text{meta} J_{\text{FF}} \approx 10 \text{ Hz}, F^6 \text{ or } 7 \)), 15.9 (ddd, \( \text{ortho} J_{\text{FF}} \approx 19 \text{ Hz}, \text{meta} J_{\text{FF}} \approx 8 \text{ Hz}, F^6 \text{ or } 7 \)). \( ^{31}P{\{^1H\}} \) NMR ((CD\(_3\))\(_2\)CO), \( \delta 13.6 \text{ (s). MS, } m/z (I_{\text{rel}}, \%) \): 444 [M]\(^+\) (6), 200 [M–C\(_{10}\)F\(_4\)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-dioxatetracene-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 20ºC 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. \( ^1H \) NMR (CDCl\(_3\)), \( \delta 7.73–7.64 \text{ (m, 6H, C}_6\text{H}_5\)), 7.64–7.56 (m, 3H, C\(_6\)H\(_5\)), 7.55–7.46 (m, 6H, C\(_6\)H\(_5\)), 7.02–6.97 (m, 4H, C\(_6\)H\(_4\)). \( ^{19}F \) NMR (CDCl\(_3\)), \( \delta 24.0 \text{ (d, } \text{para} J_{\text{FF}} = 13.6 \text{ Hz, } F^6 \text{ or } 11\)), 21.6 (d, \( \text{para} J_{\text{FF}} = 13.6 \text{ Hz, } F^6 \text{ or } 11\)). \( ^{31}P{\{^1H\}} \) NMR (CDCl\(_3\)), \( \delta 14.8 \text{ (s). MS, } m/z (I_{\text{rel}}, \%) \): 577 [M+H]\(^+\) (2), 547 [M–H–CO]\(^+\) (25), 262 [M–C\(_{16}\)H\(_2\)F\(_2\)O\(_5\)]\(^+\) (52). HRMS for C\(_{34}\)F\(_4\)H\(_{19}\)O\(_3\)P [M+H]\(^+\): calcd. 577.1011, found [M+H]\(^+\) 577.1310.

Acknowledgements

Authors are grateful to Russian Foundation of Basic Research for the financial support (grant 09-03-00248).

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