Synthesis of diphenyl(X)phosphonium betaines (X = CH_3, C_6H_5, 2,5-$F_2C_6H_3$) 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

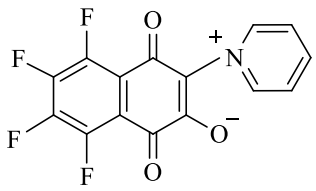
Betaines 5,6,7,8-tetrafluoro-3-(triphenyl-λ^5-phosphanylidene)-1,2,3,4-tetrahydronaphthalene-1,2,4-trione, 5,6,7,8-tetrafluoro-3-(methyldiphenyl-λ^5-phosphanylidene)-1,2,3,4-tetrahydronaphthalene-1,2,4-trione, and 3-[(2,5-difluorophenyl)diphenyl-λ^5-phosphanylidene]-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydronaphthalene-1,2,4-trione have been synthesized via fluorine substitution in the quinone ring of hexafluoro-1,4-naphthoquinone by tertiary phosphines RPh_2P (R = Me, Ph, 2,5-$F_2C_6H_3$) 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-λ^5-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 **1**, 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-(triphenylphosphoranylidene)-1,2,4(3*H*)-naphthalenetrione in a 68% yield.[2,3]



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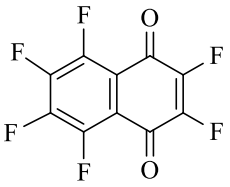

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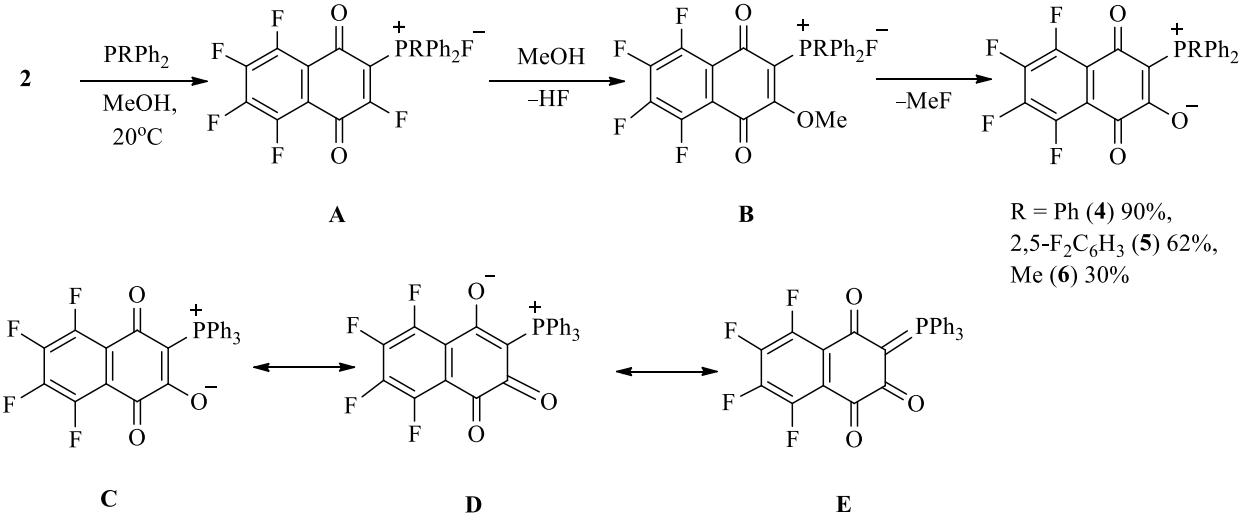
In this connection, in the present work we report the synthesis of 5,6,7,8-tetrafluoro-1,4-naphthoquinone phosphonium betaines via phosphoniodefluorination of quinone **2** and 2,5,6,7,8-pentafluoro-1,4-naphthoquinone **3** by the action of phosphines RPh_2P (R = Me, Ph, 2,4-$F_2C_6H_3$) and methanol. 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

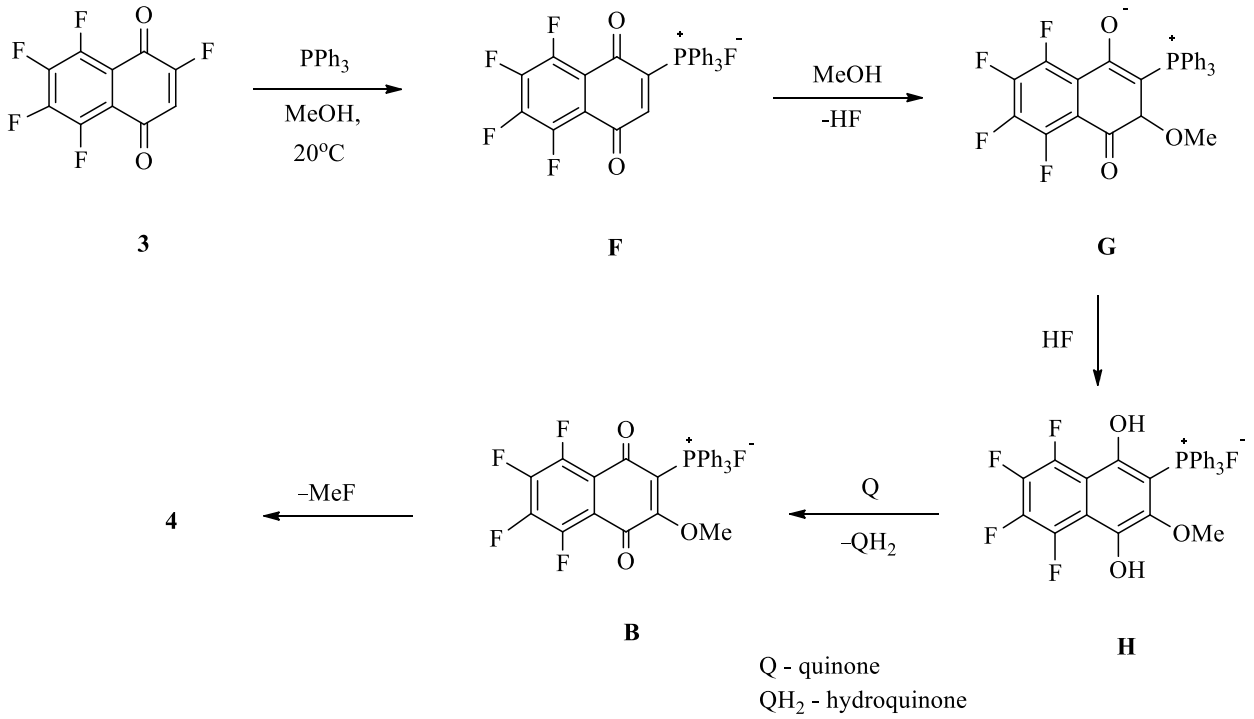
Interaction of quinone **2** with triphenylphosphine in methanol gave in a 90% yield a betaine – 5,6,7,8-tetrafluoro-3-(triphenyl-λ^5-phosphanylidene)-1,2,3,4-tetrahydronaphthalene-1,2,4-trione **4** – whose electronic structure could be depicted in a first approximation by a resonance of structures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



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-λ^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-λ^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).



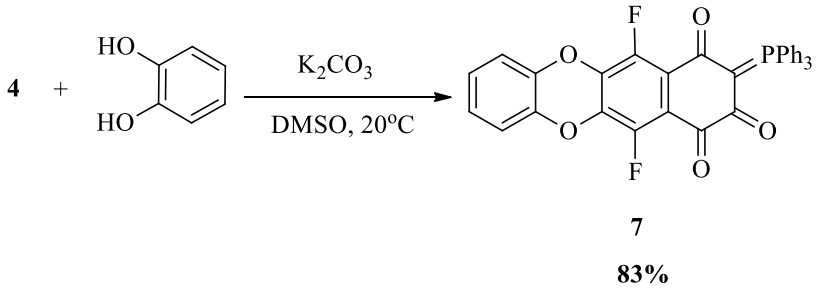
Scheme 2. Formation of betaine **4** from quinone **3**.

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**.

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).



7

83%

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

Its structure is confirmed by the presence in the ^{19}F NMR spectrum of two doublets with $^{para}J_{FF}$ = 13.6 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 $^{ortho}J_{FF}$ = 19−20 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 δ 22–24 for F^5 and F^8 and 11–17 ppm for F^6 and F^7, their spin coupling structures being typical for *ortho* disubstituted tetrafluorobenzenes ($^{ortho}J_{FF} \approx 19$, $^{meta}J_{FF}$ = 8–10, $^{para}J_{FF}$ = 13.6–13.8 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_6F_6 and internal H_3PO_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 destilled. DMSO was dried by molecular sieves 3Å. Triphenylphosphine was crystallized from diethyl ether.

5,6,7,8-Tetrafluoro-3-(triphenyl-λ^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 ºC. 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 ($(CD_3)_2CO$), δ 7.8 (m, 6H, CH), 7.7 (m, 3H, CH), 7.6 (m, 6H, CH). ^{19}F NMR ($(CD_3)_2CO$), δ 22.4 (ddd, $^{ortho}J_{FF} \approx 19$ Hz, $^{meta}J_{FF} \approx 10$ Hz, $^{para}J_{FF} = 13.8$ Hz, $F^{5\text{ or }8}$), 21.8 (ddd, $^{ortho}J_{FF} \approx 19$ Hz, $^{meta}J_{FF} \approx 8$ Hz, $^{para}J_{FF} = 13.8$ Hz, $F^{5\text{ or }8}$), 15.9 (ddd, $^{ortho}J_{FF} \approx 19$ Hz, $^{meta}J_{FF} \approx 10$ Hz, $F^{6\text{ or }7}$), 11.0 (ddd, $^{ortho}J_{FF} \approx 19$ Hz, $^{meta}J_{FF} \approx 8$ Hz, $F^{6\text{ or }7}$). ^{31}P{^{1}H} NMR ($(CD_3)_2CO$), δ 15.3 (s). MS, *m*/*z* ($I_{rel.}$, %): 506 $[M]^+$ (14), 477 $[M-H-CO]^+$ (48), 262 $[M-C_{10}F_4O_3]^+$ (100). HRMS for $C_{28}F_4H_{15}O_3P$ $[M]^+$: 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 ºC 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-λ^5-phosphanylidene]-5,6,7,8-tetrafluoro-1,2,3,4-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 ºC. 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 ($(CD_3)_2CO$, CH_2Cl_2), δ 7.92−7.81 (m, 4H, C_6H_5), 7.80−7.71 (m, 2H, C_6H_5), 7.69−7.58 (m, 4H, C_6H_5), 7.51 (m, 1H, $C_6F_2H_3$), 7.29 (m, 1H, $C_6F_2H_3$), 7.05 (m, 1H, $C_6F_2H_3$). ^{19}F NMR ($(CD_3)_2CO$, CH_2Cl_2), δ 61.8 (m, 1F, $C_6F_2H_3$), 46.7 (m, 1F, $C_6F_2H_3$), 23.6 (ddd, $^{ortho}J_{FF} \approx 19$ Hz, $^{meta}J_{FF} \approx 10$ Hz, $^{para}J_{FF} = 13.8$ Hz, $F^{5\text{ or }8}$), 22.7 (ddd, $^{ortho}J_{FF} \approx 19$ Hz, $^{meta}J_{FF} \approx 9$ Hz, $^{para}J_{FF} = 13.8$ Hz, $F^{5\text{ or }8}$), 17.1 (ddd, $^{ortho}J_{FF} \approx 19$ Hz, $^{meta}J_{FF} \approx 10$ Hz, $F^{6\text{ or }7}$), 12.5 (ddd, $^{ortho}J_{FF} \approx 19$ Hz, $^{meta}J_{FF} \approx 9$ Hz, $F^{6\text{ or }7}$). ^{31}P{^{1}H} NMR ($(CD_3)_2CO$, CH_2Cl_2), δ 9.4 (dd, $^3J_{PF} \sim {}^4J_{PF} = 3$ Hz). MS, *m*/*z* ($I_{rel.}$, %): 542 $[M]^+$ (7), 513 $[M-H-CO]^+$ (28), 298 $[M-C_{10}F_4O_3]^+$ (100). HRMS for $C_{28}F_6H_{13}O_3P$ $[M]^+$: calcd. 542.0501, found 542.0490.

5,6,7,8-Tetrafluoro-3-(methyldiphenyl-λ^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 ºC 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 ºC. ^{1}H NMR ($(CD_3)_2CO$), δ 7.92−7.81 (m, 4H, C_6H_5), 7.76−7.68 (m, 2H, C_6H_5), 7.66−7.58 (m, 4H, C_6H_5), 2.6 (d, $^2J_{PH} = 14.2$ Hz, 3H, CH_3). ^{19}F NMR ($(CD_3)_2CO$), δ 22.5 (ddd, $^{ortho}J_{FF} \approx 19$ Hz, $^{meta}J_{FF} \approx 10$

Hz, $^{para}J_{FF}$ = 13.8 Hz, $F^{5 \text{ or } 8}$), 21.8 (ddd, $^{ortho}J_{FF} \approx 19$ Hz, $^{meta}J_{FF} \approx 8$ Hz, $^{para}J_{FF}$ = 13.8 Hz, $F^{5 \text{ or } 8}$), 15.9 (ddd, $^{ortho}J_{FF} \approx 19$ Hz, $^{meta}J_{FF} \approx 10$ Hz, $F^{6 \text{ or } 7}$), 11.1 (ddd, $^{ortho}J_{FF} \approx 19$ Hz, $^{meta}J_{FF} \approx 8$ Hz, $F^{6 \text{ or } 7}$). $^{31}P\{^{1}H\}$ NMR ($(CD_3)_2CO$), δ 13.6 (s). MS, *m/z* (I_{rel}., %): 444 $[M]^+$ (6), 200 $[M–C_{10}F_4O_3]^+$ (62). HRMS for $C_{23}F_4H_{13}O_3P$ $[M]^+$: calcd. 444.0533, found 444.0535.

6,11-Difluoro-9-(triphenyl-λ^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 20 ºC 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 ($CDCl_3$), δ 7.73–7.64 (m, 6H, C_6H_5), 7.64−7.56 (m, 3H, C_6H_5), 7.55−7.46 (m, 6H, C_6H_5), 7.02−6.97 (m, 4H, C_6H_4). ^{19}F NMR ($CDCl_3$), δ 24.0 (d, $^{para}J_{FF}$ = 13.6 Hz, $F^{6 \text{ or } 11}$), 21.6 (d, $^{para}J_{FF}$ = 13.6 Hz, $F^{6 \text{ or } 11}$). $^{31}P\{^{1}H)$ NMR ($CDCl_3$), δ 14.8 (s). MS, *m/z* (I_{rel}., %): 577 $[M+H]^+$ (2), 547 $[M−H−CO]^+$ (25), 262 $[M−C_{16}H_5F_2O_5]^+$ (52). HRMS for $C_{34}F_2H_{19}O_5P$ $[M+H]^+$: calcd. 577.1011, found $[M+H]^+$ 577.1310.

Acknowledgements

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References

1. (a) Nevinsky, G. A; Zakharova, O. D.; Goryunov, L. I.; Troshkova, N. M.; Shteingarts, V. D. RU Patent 2387635, 2008. (b) Zakharova, O. A.; Goryunov, L. I.; Troshkova, N. M.; Ovchinnikova, L. P.; Shteingarts, V. D.; Nevinsky, G. A. *Eur. J. Med. Chem.* **2010**, *45*, 270. Zakharova O. D.; Ovchinnikova L. P.; Goryunov L. I.; Troshkova N. M.; Shteingarts V. D.; Nevinsky G. A. *Eur. J. Med. Chem.* **2010**, *45*, 2321.
2. Loskutov, V. A.; Mamatyuk, V. I.; Beregovaya, I. V. *Russ. Chem. Bull*. **1999**, *48*, 371.
3. Makoto, M.; Yorinobu, Y.; Kazuaki, S.; Kozo, B.; Tsunekatsu, S. Jpn. Pat. Appl. 53–147050 1978.
4. Goryunov, L. I.; Troshkova, N. M.; Nevinsky, G. A.; Shteingarts, V. D. *Russ. J. Org. Chem*. **2009**, *45*, 835.
5. Finley, K. T. In *The chemistry of the quinonoid compounds*; Patai, S. J. Ed.; Wiley&Sons Ltd., 1974; Vol 2, pp 844–1145.
6. Shteingarts, V. D.; Osina, O. I.; Kostina, N. G.; Yakobson, V. D. *Zh. Org. Khim*. **1970**, *6*, 833.

7. Yakobson, V. D.; Shteingarts, V. D.; Vorozhtsov-jun., N. N. *Zh. Vses. Khim. Ob. im. D. I. Mendeleeva* **1964**, *9*, 702.
8. Goryunov, L. I.; Grobe, J.; Zhivetyeva, S. I.; Shteingarts, V. D.; Mews, R. 16th European Symposium on Fluorine Chemistry, Ljubljana, Slovenia, July 18–23, 2010: Book of Abstracts, P1-58.

