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Phosphonium salts with a dihydroxynaphthyl substituent: versatile synthesis and evaluation of antimicrobial activity

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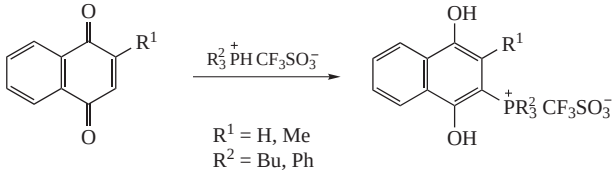
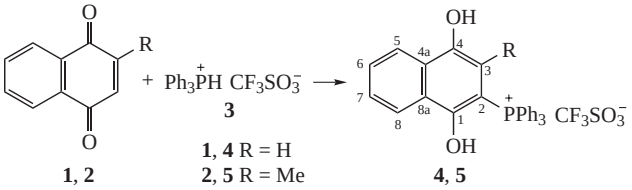
(1,4-Dihydroxynaphthalen-2-yl)phosphonium salts were obtained by reaction of P–H phosphonium salts with substituted 1,4-naphthoquinones. Some representatives of this series possess high activity against Gram-positive bacteria (*Staphylococcus aureus* ATCC 209p, *Bacillus cereus* ATCC 8035).



New means to obtain functionally substituted phosphonium salts are topical due to their high practical importance for the creation of materials with valuable optical properties,[1] catalysts[2] and ionic liquids.[3] Recently, much attention was focused on the biological properties of phosphonium salts which manifest antioxidant[4] and antimicrobial activities[5] and are tumor growth inhibitors (owing to the capability to selectively penetrate through cell membranes and be accumulated in the mitochondria of tumor cells, thus suppressing their functions).[6] Analysis of literature shows that simple or general catalytic methods for the synthesis of functionalized arylphosphonium salts are lacking. The known methods[7] mainly include treatment of triphenylphosphine with various alkyl and aryl halides, catalytic cross-coupling reactions,[8] as well as other less common approaches (for a review, see ref. 8).

We have recently found that 1,2-naphthoquinones react with tertiary and secondary phosphines to give phosphobetaines containing a P–C bond, which can be precursors of phosphonium salts.[9] In this study we attempted to apply this method to 1,4-naphthoquinone derivatives. However, the reaction of 2-methyl-1,4-naphthoquinone **2** with triphenylphosphine did not provide a new P–C bond formation but instead resulted in slow oxidation of phosphine to phosphine oxide (^{31}P NMR). In view of this, we modified the procedure, *viz.*, 1,4-naphthoquinones **1** and **2** were coupled with phosphonium salts containing a reactive P–H bond,† obtained *in situ* from trialkyl(aryl)phosphines and trifluoromethanesulfonic acid using the known technique.[10] This approach really proved to be efficient in the case of triphenylphosphonium salt **3** and afforded phosphonium salts **4** and **5** in nearly quantitative yields (Scheme 1).‡ The reaction occurs under mild conditions (CH_2Cl_2, 20 °C, 15 min). The formation of 1,4-dihydroxynaphthylphosphonium moiety and a P–C bond follows from the changes in the chemical shift and multiplicity of the phosphorus atom signal in the ^{31}P NMR spectra of the reaction products. Unlike the starting P–H phosphonium salt **3**, the final tetraarylphosphonium salts **4** and **5** do not have a direct coupling constant from the proton and



Scheme 1

† *Triphenylphosphonium trifluoromethylsulfonate* **3**. Trifluoromethanesulfonic acid (0.16 ml, 1.89 mmol) was added dropwise with stirring to a solution of triphenylphosphine (0.5 g, 1.89 mmol) in CH_2Cl_2 (5.5 ml). The mixture was stirred for 1 h. The resulting salt was further used without isolation.

Tributylphosphonium trifluoromethylsulfonate **6**. A solution of CF_3SO_3H (0.32 ml, 3.63 mmol) was added dropwise to a solution of Bu_3P (0.73 g, 3.63 mmol) in CH_2Cl_2 (8 ml) with stirring, cooling in a water bath and intense bubbling of dry argon. The mixture was stirred for 30 min. The resulting salt was further used without isolation. $^{31}P/^{31}P\{^1H\}$ NMR (242.9 MHz, CH_2Cl_2) δ: 13.8 [dm (s), $^1J_{PH}$ 477.0 Hz].

‡ *(1,4-Dihydroxynaphthalen-2-yl)triphenylphosphonium trifluoromethylsulfonate* **4**. A solution of 1,4-naphthoquinone (0.30 g, 1.89 mmol) in CH_2Cl_2 (7 ml) was added dropwise to a solution of triphenylphosphonium triflate **3** (0.78 g, 1.89 mmol) in CH_2Cl_2 (5.5 ml) with constant stirring and intense bubbling of dry argon. After 24 h of standing the dark-brown solution was evaporated under reduced pressure (14 Torr) to give a brown precipitate of **4**, which was washed with 15 ml of hexane. Yield 1.02 g (95%), mp 89–93 °C (decomp.).

(1,4-Dihydroxy-3-methylnaphthalen-2-yl)triphenylphosphonium trifluoromethylsulfonate **5**. A solution of 2-methyl-1,4-naphthoquinone (0.28 g, 1.66 mmol) in CH_2Cl_2 (7 ml) was added dropwise to a solution of triphenylphosphonium triflate **3** (0.68 g, 1.66 mmol) in CH_2Cl_2 (5 ml) with intense bubbling of dry argon. After 24 h of standing the orange reaction mixture was evaporated under reduced pressure (14 Torr) to give a pink precipitate of **5**, which was purified by recrystallization from the mixture of acetone–diethyl ether–light petroleum (1:2:3). Yield 0.75 g (78%), mp 174–176 °C.

(1,4-Dihydroxynaphthalen-2-yl)tributylphosphonium trifluoromethylsulfonate **7**. A solution of 1,4-naphthoquinone (0.30 g, 1.90 mmol) in CH_2Cl_2 (8 ml) was added dropwise to a solution of tributylphosphonium triflate **6** (0.67 g, 1.90 mmol) in CH_2Cl_2 (4 ml) with stirring and intense bubbling of dry argon. After 24 h of standing the dark-brown reaction mixture was evaporated under reduced pressure (12 Torr) to give dark-green oil, which was crystallized during the storage under diethyl ether–hexane (15 ml, 1:2). The crystalline precipitate of **7** was filtered and dried *in vacuo* (14 Torr). Yield 0.92 g (96%), mp 128 °C.

For spectral characteristics of compounds **4**, **5** and **7**, see Online Supplementary Materials.