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Synthesis of halodifluoromethyl-substituted phosphines

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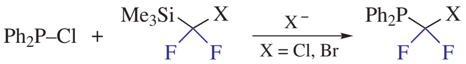
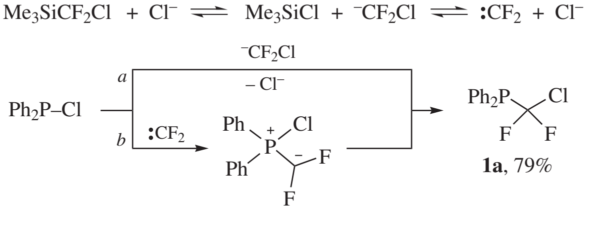
Three phosphines bearing halodifluoromethyl group were obtained starting from chlorodiphenylphosphine. Silicon reagents Me_3SiCF_2X (X = Cl, Br) were used to install chloro- or bromodifluoromethyl group to the phosphorus atom. Iododifluoromethyl-substituted phosphine was prepared by bromine/iodine exchange.



Organophosphorus compounds bearing a fluorinated substituent can find applications in medicinal chemistry[1] and as ligands for transition metals.[2] In contrast to well khown derivatives of phosphorus(V) such as phosphonates and phosphine oxides,[3] phosphines having a fluoroalkyl group at phosphorus have been poorly investigated. Typically, these compounds are prepared either by nucleophilic substitution at phosphorus[4] or by electrophilic fluoroalkylation of the P–H or P–Si bonds.[5] However, these methods are difficult to apply for the synthesis of phosphines containing a halodifluoromethyl group (R_2PCF_2X, X = Cl, Br, I). Among these compounds, only one phosphine, Ph_2PCF_2Br, was previously obtained from highly air sensitive silyl phosphine and dibromodifluoromethane.[6] Herein we report that such phosphines can be readily prepared by insertion of the difluoromethylene fragment into phosphorus–halogen bond.

Our approach is based on application of silicon reagents Me_3SiCF_2X, which have been demonstrated to serve as good sources of the CF_2 unit.[7,8] Thus, the reaction of chlorodiphenylphosphine with chloro-substituted silane Me_3SiCF_2Cl[9] was performed in the presence of 10 mol% benzyltriethylammonium chloride in toluene at 100 °C affording phosphine **1a** in 79% yield (Scheme 1).[†]



Scheme 1 *Reagents and conditions*: $BnNEt_3Cl$ (10%), PhMe, 100 °C, 3 h.

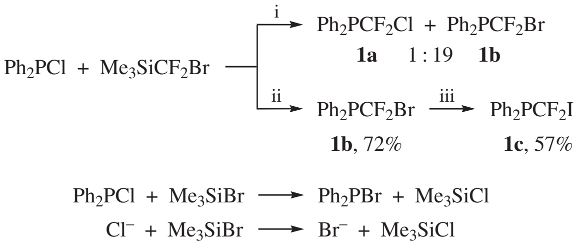
According to the proposed mechanism (see Scheme 1), the reaction likely starts from the activation of the silane by chloride ion to generate small equilibrium concentrations of chlorodifluoromethyl carbanion and difluorocarbene.[10] The chlorophosphine can undergo typical nucleophilic substitution with the carbanionic species (pathway *a*). Alternatively, the lone pair of phosphine can attack at difluorocarbene to generate ylide-type intermediate followed by 1,2-migration of the chlorine atom (pathway *b*).

When chlorodiphenylphosphine was combined with bromo(difluoromethyl)silane Me_3SiCF_2Br[11] in the presence of tetrabutylammonium bromide, a mixture of chloro- and bromo-containing phosphines **1a**,**b** was formed (Scheme 2). Rewardingly, when bromotrimethylsilane (0.5 equiv.) was applied as an additional reagent, phosphine **1b** was formed as a single product, and it was isolated in 72% yield.[‡] We believe that the role of bromosilane is to scavenge chloride owing to stronger Si–Cl bond compared to Si–Br bond. Correspondingly, chlorine/bromine exchange can occur either with starting phosphine or with resulting halide anion.

Attempts to prepare iododifluoromethyl-substituted phosphine **1c** directly from chloropdiphenylphosphine were unsuccessful. However, phosphine **1c** was obtained from **1b** by heating at 80 °C

[†] *(Chlorodifluoromethyl)diphenylphosphine* **1a**. A screw-cap tube containing benzyltriethylammonium chloride (23 mg, 0.1 mmol) was evacuated and filled with argon. Then, toluene (1 ml), Ph_2PCl (180 µl, 1 mmol), Me_3SiCF_2Cl[9(*a*)] (190 µl, 1.2 mmol) were successively added. The tube was tightly closed and heated on an oil bath at 100 °C for 3 h, and then was allowed to cool to room temperature. For the work-up, the mixture was transferred into a round bottom flask. The solvent was evaporated under vacuum, and the flask was filled with argon. The residue was washed with degassed hexanes (3 × 1 ml), the collected hexane extracts were passed through short silica gel pad (a Pasteur pipette filled with 1.5 cm layer of silica gel), washing the pad with degassed hexanes (10 ml) (during the silica gel purification, the eluate was collected into a flask under stream of argon). The solution was concentrated, and the residue was dried under vacuum. Yield 206 mg (79%). Colourless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.40–7.55 (m, 6 H), 7.68 (t, 4 H, *J* 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 128.9 (d, *J* 7.8 Hz), 130.7, 130.9 (dt, *J* 12.6, 3.1 Hz), 134.3 (td, *J* 329.8, *J* 51.6 Hz), 134.4 (d, *J* 21 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –47.6 (d, *J* 72.9 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ: 22.2 (t, *J* 72.9 Hz). HRMS (ESI), *m*/*z*: 287.0197, 289.0170 [M + O + H] (calc. for $C_{13}H_{11}F_2POCl$, *m*/*z*: 287.0199, 289.0170).

[‡] *(Bromodifluoromethyl)diphenylphosphine* **1b**.[6] A screw-cap tube containing tetrabutylammonium bromide (32 mg, 0.1 mmol) was evacuated and filled with argon. Then, toluene (1 ml), Ph_2PCl (180 µl, 1 mmol), Me_3SiCF_2Br[11(*a*)] (185 µl, 1.2 mmol), and Me_3SiBr (65 µl, 0.5 mmol) were successively added. The tube was tightly closed, heated on an oil bath at 100 °C for 3 h, and then was allowed to cool to room temperature. The work-up was similar to that for compound **1a**. Yield 218 mg (72%). Colourless oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.40–7.55 (m, 6 H), 7.68 (t, 4 H, *J* 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 128.2 (td, *J* 342.5, 64.9 Hz), 128.9 (d, *J* 7.8 Hz), 130.7, 131.2 (dt, *J* 13.2, 3.1 Hz), 134.4 (d, *J* 21 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –43.4 (d, *J* 66.5 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ: 27.6 (t, *J* 66.5 Hz).



Scheme 2 *Reagents and conditions*: i, Bu_4NBr (10%), PhMe, 100 °C, 3 h; ii, Bu_4NBr (10%), PhMe, Me_3SiBr (0.5 equiv.), 100 °C, 3 h; iii, NaI (3 equiv.), DME, 80 °C, 4 h.

with excess of sodium iodide in 1,2-dimethoxyethane (DME) for 4 h (Scheme 2).[§]

Owing to the presence of perhalogenated substituents, the basicity of the phosphorus atom is strongly decreased compared to conventional phosphines. For example, for phosphine **1a**, we have not been able to obtain its protonated tetrafluoroborate salt (upon treatment with ethereal hydrofluoroboric acid), and its borane complex was unstable at room temperature. At the same time, phosphines **1a–c** are air-sensitive oils which should be treated under inert atmosphere using degassed solvents. In fact, they undergo rapid oxidation with oxygen if their solutions are concentrated on a regular rotary evaporator followed by filling the flask with air.

In summary, a method for the synthesis of phosphines bearing halodifluoromethyl group is described. Chloro- and bromodifluoromethyl-substituted organophosphorus compounds were obtained by insertion of the difluoromethylene fragment into phosphorus–halogen bond.

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[§] *(Iododifluoromethyl)diphenylphosphine* **1c**. In a screw-cap tube, sodium iodide (450 mg, 1.5 mmol) was dried under vacuum with a heat gun, and the tube was cooled down and filled with argon. A solution of Ph_2PCF_2Br (157 mg, 0.5 mmol) in 1,2-dimethoxyethane (0.9 ml) was added. The tube was tightly closed and heated on an oil bath at 80 °C for 4 h. The work-up was similar to that for compound **1a**. Yield 101 mg (57%). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42–7.52 (m, 6H), 7.69 (t, 4H, *J* 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 110.3 (td, *J* 348.8, 70.6 Hz), 129.0 (d, *J* 8.0 Hz), 130.7, 132.1 (dt, *J* 13.8, 3.4 Hz), 134.5 (d, *J* 20.7 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –39.3 (d, *J* 69.7 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ: 38.0 (t, $^2J_{PF}$ 69.7 Hz). HRMS (ESI), *m/z*: 378.9543 [M+O+H] (calc. for $C_{13}H_{11}F_2IPO$, *m/z*: 378.9555).