EurJIC
European Journal of Inorganic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Inorg. Chem.* 10.1002/ejic.201900165

Link to VoR: http://dx.doi.org/10.1002/ejic.201900165

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10.1002/ejic.201900165

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Synthesis and properties of the fluoromethylating agent – (fluoromethyl)triphenylphosphonium iodide

Marco Reichel,[a] Jörn Martens,[a] Eduart Wöllner,[a] Laura Huber,[a] Andreas Kornath,[a] Konstantin Karaghiosoff* [a]

Abstract: (fluoromethyl)triphenylphosphonium iodide has been prepared in a simple and high yield synthesis. The salt was characterized by vibrational, NMR-spectroscopy and a single crystal X-ray structure analysis. The salt crystallizes in an orthorhombic space group *P*na2$_1$ with four formula units in the unit cell. The experimental data are discussed together with quantum chemically calculated values. The title compound is the first example of a phosphonium salt containing a P-CH_2F moiety. Hydrogen bonding in the crystal of the fluoromethyl phosphonium iodide is discussed.

Introduction

Nowadays, around 20 % of all pharmaceuticals and 30 - 40% of all agrochemicals contain fluorine.[1] Due to their unique physical, chemical and biological properties, fluorinated organic compounds are widely used in drugs, agrochemicals, dyes, polymers or surfactants.[2] Fluoromethylated compounds, especially compounds with a monofluoromethyl moiety –CH_2F are of considerable pharmaceutical importance.[3] Many of these molecules are biologically active (Figure 1).[1,4] Afloqualone (**1**) is a muscle-relaxant and sedative with clinical use.[5] Sevofluoran (**2**) is a volatile anesthetic with great significance in pediatric anesthesia due to its good hypnotic, only weak analgesic and muscle relaxating properties.[4,6] Fluticasone propionate (**3**) – a widely used drug against inflammatory diseases and as analgesic in the treatment of certain cancers[1] – is one of the industrially most important drugs. Beta-fluorinated amino acids (**4**, **6**) act as so called "suicide substrates" being able to inactivate decarboxylase enzymes and can be used against Parkinson diseases.[7] The Androsta-1,4-diene-3,17-dione (**5**) acts as aromatase inhibitor and is suitable for the treatment of estrogen-dependent diseases such as anovulatory infertility, prostate hyperplasia, mammacarcinomia and many more.[8]

There are only a few possible synthetic methods to generate the fluoromethyl group reported in literature. One strategy starts from a suitably substituted functionality –CH_2X (X = Cl, Br, I or another electronegative group) and involves the exchange of X by F using CsF or an appropriate reagent delivering fluoride anions. A second pathway is the direct fluoromethylation using a fluoromethylating agent like CH_2FBr or CH_2FI.[9] Recently a nucleophilic fluoromethylation strategy involving the fluoromethyl anion as the lithium derivative was reported to yield α-fluoromethyl alcohols, -ketones and -amines.[10]

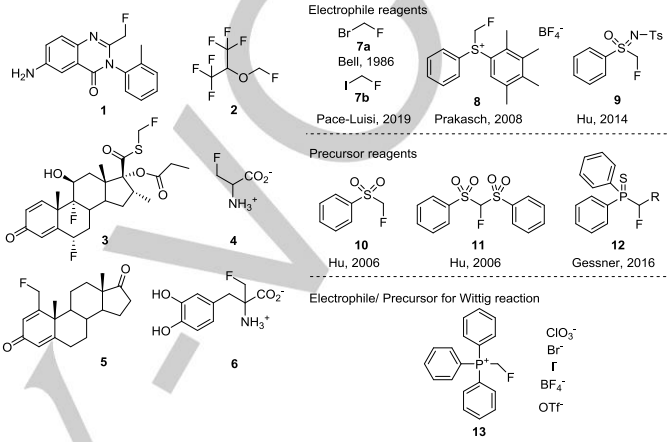

Figure 1. Representative CH_2F-containing drugs (left). Fluoromethylating agents (right).

Very recently new techniques for the transfer of "CHF" and "CIF" units to organic substrates starting from diarylfluoromethyl sulfonium salts or CH_2FI in combination with the use of special bases have been reported.[11] In addition to the fluoromethyl halides CH_2FBr and CH_2FI other more effective fluoromethylating agents have been developed in the last years (Figure 1).[3,10,12] *Emilia Leitao et al*. reported, that monofluoromethyl-S-phenyl-S-2,3,4,5-tetramethylphenyl sulfonium tetrafluoroborate, mono-fluoromethyl ammonium salts and monofluoromethyl-phosphonium salts **13** (Figure 2) are suitable for monofluoromethylation. Thus, fluoromethylation of the precursor **14** with the phosphonium salts **13** proceeds under mild conditions (room temperature) with caesium carbonate yielding Fluticasone **3**. This synthesis avoids the use of ozone depleting CH_2FBr.[12c] Furthermore, the phosphonium cation in **13** is used to generate a Wittig reagent with a CHF-group attached to phosphorus. Reaction with carbonyl compounds results in the formation of fluoroethenes. This route has been applied to synthesize isofagomine analogs as glucocerebrosidase modulator having therapeutic uses[13] or SSAO inhibitors.[14] In the special case of **16**, formation of the C=C double bond is followed by hydrogen shift, resulting in an overall fluoromethylation at the carbonyl carbon atom (Figure 2).[1] The fluoromethyl triphenylphosphonium reagent **13** can be prepared by a series of different routes.[15] The synthesis of **13**, X = BF_4, involves for instance fluoromethylation of triphenylphosphine by the sulfonium derivative described by *Prakash*.[3] The iodide **13**, X = I, is readily obtained by

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fluoromethylation of triphenylphosphine with CH_2FI. Unfortunately this straightforward reaction requires long reaction times (e.g. 63 h reflux in benzene).[4,13,15] In particular, the long reaction time makes the synthesis of larger amounts of **13** (X = I) problematic.[16] In the course of our recent investigations on fluoromethylating agents we recognized that to our best knowledge structural deformations on PCH_2F moiety has not been reported in literature. This prompted us to investigate the phosphonium salt more closely.

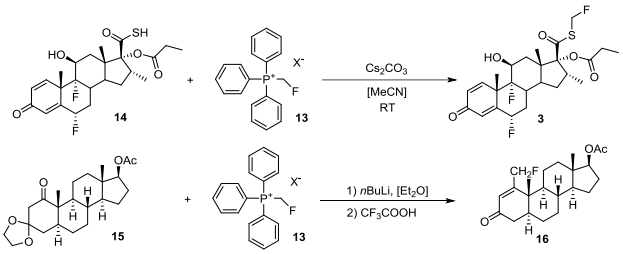

Figure 2. Reaction of monofluoromethyl phosphonium salt **13** with Andostrane derivate **14** and **15**.

Results and Discussion

Synthesis and Properties

For the synthesis of **13** (X = I) we choose the reaction of triphenylphosphine with CH_2FI. The specific challenge of this fluoromethylation of triphenylphosphine with CH_2FI is the slow reaction rate. We observed, that heating of the reaction mixture in toluene at 110 °C for a prolonged time (63 h) results in the formation of a brown solution, most probably due to decomposition of CH_2FI. However, if a solution of triphenylphosphine and the equimolar amount of CH_2FI is heated in a pressure tube to temperatures up to 120 °C, the reaction time is reduced considerably (6 h in DME) yielding **13** (X = I) up to 61 %. Different reaction solvents and times have been tested (Table 1). Temperatures higher than 120 °C result in decomposition of CH_2FI. Reaction time can be further reduced by using an excess of CH_2FI. The excess of CH_2FI can be readily recovered by distillation during workup (see Experimental). The best conditions with DME or acetonitrile as solvent (entries 8 and 9) yield the phosphonium iodide **13** as a colorless microcrystalline powder (yield up to 99.8 %) in a high purity as determined by ^1H and ^{19}F NMR spectroscopy

Table 1. Fluoromethylation of triphenylphosphine to **13** (X = I) under various reaction conditions.

Entry	Solvent	t[h]	T[°C]	X(eq)	pressure	Yield [%]
1	Pentane	6	36	1	No	10
2	Diethylether	6	35	1	No	29
3	DME/Dioxane	6	85	1	No	37
4	DME	12	84	1	No	60
5	Toluene	63	110	1	No	70
6	Acetonitrile	6	120	1	Yes	59
7	DME	6	120	1	Yes	61
8	Acetonitrile	4	120	3	Yes	94
9	DME	3	120	3	Yes	99.8

The phosphonium iodide **13** (X = I) is slightly light sensitive changing its color from colorless to slightly brownish on prolonged exposure to light. The differential thermal analysis (DTA) curve of **13** (X = I) is shown in Figure 3. It shows the melting point at 170 °C with an onset point of 155 °C (the melting behavior was confirmed by DSC measurement). Literature values are in range of 168 – 171 °C.[15d,16] The phosphonium iodide **13** is reported to decompose at its melting point (Figure 3), changing its color to brown. NMR spectroscopic (in CD_3CN) and single X-ray analysis of the resulting brown solid shows by surprise the formation of the triphenylmethyl - phosphonium cation $Ph_3P(CH_3)^+$.[17] This cannot be explained for us, but one cannot doubt the identity.

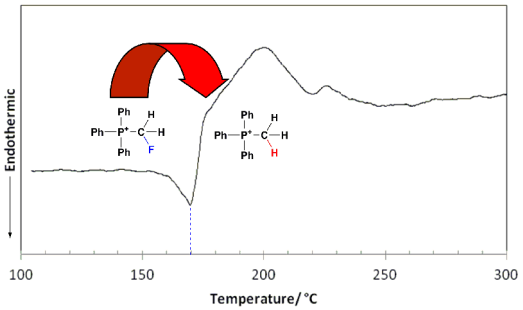

Figure 3. Thermal behavior (DTA) of **13**.

Crystal Structure

Single crystals of **13** (X = I), suitable for X-ray diffraction, were obtained by slow evaporation of an acetonitrile solution. The compound crystallizes in the orthorhombic space group *Pna*2_1 with four formula units in the unit cell. The asymmetric unit of **13** is shown in Figure 4.

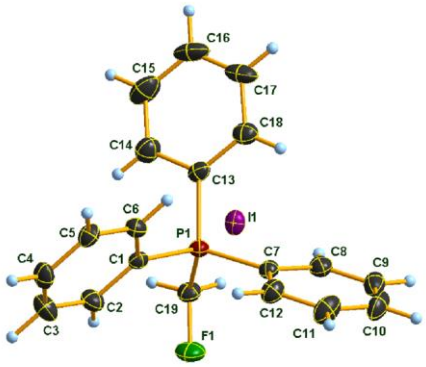

Figure 4. Molecular structure of compound **13** in the solid state, DIAMOND representation, thermal ellipsoids shown at 50 % probability level.

The phosphorus atom displays a slightly distorted tetrahedral surrounding. The phenyl moieties show a propeller like arrangement. The P1-C19 distance to the carbon atom of the CH_2F group corresponds with 1.810(4) Å to a P-C single bond.[18] The C19-F1 distance of 1.379(5) Å compares to the value of 1.399 Å (C_{sp}^3-F), found in literature.[18] The most interesting feature of the structure is the PCH_2F moiety. The P1-C19 bond length of 1.810(4) Å is elongated compared to a P-CH_3 moiety

[1.776(2) Å]. The C19-F1 bond length of 1.379(5) Å is unaffected by the phosphonium substituent and in the region of a typical C-F single bond observed for CH_2FI [1.380(17) Å] or CH_2BrF [1.377(4) Å].[19] In order to obtain information on the structural behavior of the P-CH_2F unit, weak interactions in the crystal structure of **13** (X = I) are of interest. The iodide anions show weak hydrogen bonding to the CH_2-protons of the phosphonium cation, which results in the formation of chains along the a-axis (Figure 5).

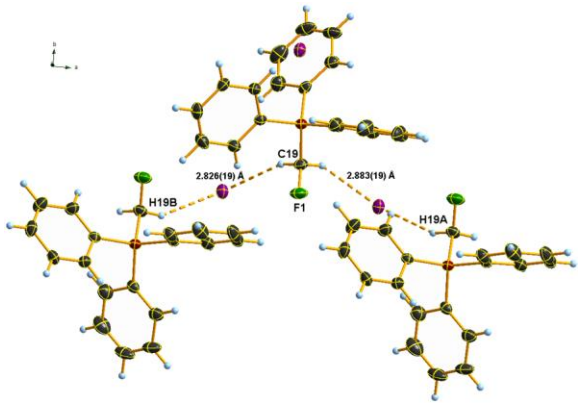

Figure 5. Hydrogen bonding in the crystal structure of compound **13**, DIAMOND representation. Thermal ellipsoids are shown at 50 % probability level. Symmetry code for the left phosphonium cation: -0,5+x, -0,5-y, z; for the left iodide anion: 1,5.-x, 0,5+y, -0,5+z; for the right phosphonium cation: 0,5+x, -0,5-y, z; for the right iodide anion: 2-x, -y, -0,5+z.

There are no significant fluorine-hydrogen interactions (shortest distance 2.51(3) Å). In contrast, the crystal structure of the related triphenylphosphonium hydroxymethyl iodide (CH_2F replaced by the bioisosteric CH_2OH)[20] is dominated by a –OH···I hydrogen bond; the interactions of I^- to the CH_2 protons are in this case (as expected) weaker (CH···I distances of 3.0923(2) and 3.2070(2) Å).[21]

Vibrational Spectra

The experimental and calculated Raman spectra of **13** in the range of 150 – 3500 cm^{-1} are shown in Figure 6. The assignments were made on the basis of literature data and quantum chemical calculations (B3LYP/ 6-311G+(d,p)) of the phosphonium cation.[22]

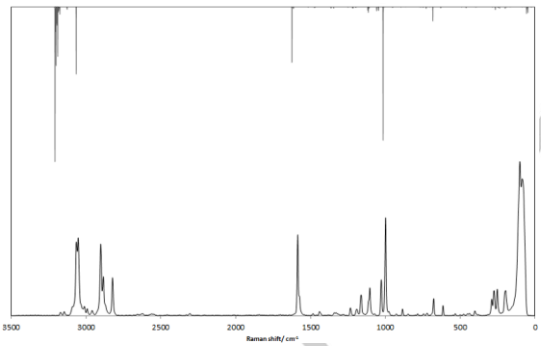

Figure 6. Experimental Raman spectrum of **13** (bottom) and calculated vibrational spectrum of the cation of **13** (top).

The characteristic line in the Raman spectra of **13** (999 cm^{-1}) corresponds to the skeleton vibration mode of the aromatic carbon atoms. The asymmetric $\nu_{as}(CH_2)$, symmetric $\nu_s(CH_2)$ and rocking $\vartheta(CH_2)$ vibration modes of the fluoromethyl group account for the lines at 2901, 2884 and 1233 cm^{-1}, respectively. The C-F stretching mode is calculated to appear at 1056 cm^{-1}, but compared to other –CH_2F compounds of poor intensity and therefore not observable in the Raman spectrum. The bands 1110 cm^{-1} ν(CF) and 719 cm^{-1} ν(CF) in the IR-spectra are assigned to the CF stretch- and PCF deformation vibration. The band at 883 cm^{-1} is assigned to the rocking vibration of the CH_2F group.

Table 2. Selected vibrational frequencies [cm^{-1}], intensities and assignments for **13** (experimental and calculated), PPh_3 and CH_2FI (FIM)

13 Experimental	**13** Calculated	PPh_3	FIM	Assignments
3064 (50)	3205 (100)		2976	$\nu_s(C_{arom}H)$, ν(CH)
3051 (52)	3191 (20)	3048		$\nu_{as}(C_{arom}H)$
2901 (47)	3125 (10)			$\nu_{as}(CH_2)$
2884 (25)	3064 (50)			$\nu_s(CH_2)$
1586 (49)	1623 (35)	1584		$\nu_{as}(C_{arom}C_{arom})$
1233 (5)	1248 (1)		1266	ϑ (CH_2), ν(CF)
1191 (11)	1195 (2)	1180		$\varsigma(C_{arom}H)$ ν(CH),
1162 (15)	1116 (2)	1158		$\nu_{as}(C_{arom}P)$
1104 (20)	1109 (5)	1095		$\nu_s(C_{arom}C_{arom})$
1028 (25)	1044 (11)	1027		$\delta(C_{arom}C_{arom})$
999 (55)	1012 (20)	1000		$\delta(C_{arom}C_{arom})$
615 (10)	628 (8)	618	561	$\delta(C_{arom}C_{arom})$, ν(CI)
290 (15)	282 (3)			$\nu_{as}(PC)$

The intensities for the Raman spectra are shown in parentheses and scaled relative to the intensity of the strongest peak in each spectrum, which is assigned to a value of 100. The symbols ν_s, ν_{as}, ϑ, ς and δ denote symmetric-, asymmetric-, rock-, scissor- and in plane vibration mode respectively.

Conclusions

In conclusion we have developed an efficient and facile synthesis method for the monofluoromethylating agent **13** (X = I) in high purity. Single crystal X-ray diffraction reveals first structural information of a phosphorus bonded CH_2F group. The P-CH_2F moiety has an elongated P-C bond compared to that of a P-CH_3 moiety whereas the C-F bond lengths of **13** (X = I) is in the region of a typical C-F single bond observed for example in CH_2FI. Stronger hydrogen bonds are resulted between CH_2F

and I^- than with the bioisoster CH_2OH moiety and I^-. The compound forms CH···I hydrogen bonded chains in the crystal along the a-axis, while only very weak fluorine hydrogen interactions are observed.

Experimental Section

Reagents and Chemicals: All compounds were handled using Schlenk techniques under dry Ar. Triphenylphosphine (BASF) was dried in *vacuo* at room temperature for 15 min and fluoroiodomethane (donation from F-Select GmbH) was distilled under inert conditions before use. Solvents were purchased from ABCR, dried and distilled before use.

NMR Spectroscopy: The samples for NMR spectroscopy were prepared under inert atmosphere using Ar as protective gas. The solvent $CDCl_3$ was dried using $CaCl_2$, distilled and stored under Ar atmosphere. Spectra were recorded on a Bruker Avance III spectrometer operating at 400.1 MHz (^{1}H), 376.4 MHz (^{19}F), 161.9 MHz (^{31}P) and 100.6 MHz (^{13}C). Chemical shifts are referred to TMS (^{1}H, ^{13}C), $CFCl_3$ (^{19}F) and 85 % H_3PO_4 (^{31}P).

Raman Spectroscopy: The samples for Raman spectroscopy were sealed in glass tubes under Argon. The Raman spectrum of **13** was recorded with a Bruker MultiRam FT Raman spectrometer using a neodymium doped yttrium aluminium garnet (Nd:YAG) laser (λ = 1064 nm) with 1074 mW.

Infrared Spectroscopy: The samples for Infrared spectroscopy were placed under ambivalent conditions without further preparation onto an ATR unit using a Perkin Elmer Spectrum BX II FT-IR System spectrometer.

Thermal analysis: Melting and / or decomposition points were detected with a Linseis DSC-PT10 instrument and with a OZM DTA 552-Ex instrument under inert atmosphere and ambivalent conditions, respectively. For the DSC, the powder sample was pelletized into an aluminium crucible with a sample weight of 1 mg. The sample was placed into the instrument chamber filled with N_2 as protective gas. The scanning temperature range was set from 293 K to 673 K at a scanning rate of 5 K min^{-1}. The DTA was recorded under ambivalent conditions. Therefore, 25 mg of the sample was filled into a tube, which was placed into the instrument. The scanning temperature range was set from 293 K to 673 K at a scanning rate of 5 K min^{-1}.

Mass Spectrometry: The samples were prepared under N_2 atmosphere. High resolution mass spectral data were acquired using a Jeol MStation Sectorfield in FAB$^+$ mode.

Elemental Analysis: The sample was prepared under N_2 atmosphere. Elemental analysis was done with a Vario EL instrument and a Metrohm 888 Titrando device.

Calculations: The calculations were performed with the Gaussian09 program.[22b] The structure was optimized and frequencies calculated at the DFT B3LYP level of theory using a 6-311G+(d,p) basis set.

Synthesis (Method A): A solution of triphenylphosphine (1.14 g, 4.33 mmol) in DME (6 mL) was inserted into a pressure tube and CH_2FI (0.879 mL, 13.0 mmol) was added quickly. The pressure tube was sealed under Ar and heated for 3 h at 120 °C. The white precipitate was separated by vacuum filtration, dried *in vacuo* yielding **13** as colourless crystalline solid (2,28 g, 99.8 %). From the filtrate, the excess of CH_2FI was recovered by distillation.

Synthesis (Method B): A solution of triphenylphosphine (1.42 g, 5.41 mmol) in acetonitrile (6 mL) was inserted into a pressure tube and CH_2FI (1.10 mL, 16.2 mmol) was added quickly. The pressure tube was sealed under Argon and heated for 4 h at 120 °C. The solvent and the excess of CH_2FI was removed using a rotary evaporator, the resulting white solid was washed with 3 × 20 mL toluene and dried *in vacuo*. Yield: 2,15 g (94 %). Excess of CH_2FI was recovered by distillation of the collected solution from the rotary evaporator.

^{1}H-NMR (400 MHz, $CDCl_3$, 26°C): δ = 7.92 – 7.83 (m, 9H), 7.77 – 7.72 (m, 6H), 6.88 (d, $^2J_{F,H}$ = 45.0 Hz, 2H, -CH_2F) ppm. ^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 26°C): δ = 136.2 (d, $^4J_{P,C}$ = 3.1 Hz, C-4), 134.5 (dd, $^2J_{P,C}$ = 10.4, $^4J_{FC}$ = 1.2 Hz, C-2), 130.9 (d, $^3J_{P,C}$ = 13.0 Hz, C-3), 114.8 (d, $^1J_{P,C}$ = 86.5 Hz, C-1), 78.3 (dd, $^1J_{F,C}$ = 197.7, $^1J_{PC}$ = 63.8 Hz, -CH_2F) ppm. ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$, 26°C): δ = 19.3 (d, $^2J_{P,F}$ = 57.6 Hz) ppm. ^{19}F{^{1}H}-NMR (376 MHz, $CDCl_3$, 26°C): δ = -242.87 (d, $^2J_{P,F}$ = 57.6 Hz) ppm. ^{19}F-NMR (376 MHz, $CDCl_3$, 26°C): δ = -242.87 (dt, $^2J_{P,F}$ = 57.6, $^2J_{F,H}$ = 45.0 Hz) ppm. Raman: (see Table 2). FT-IR (ATR): $\tilde{\nu}$ = 3050(w), 2896(m), 2879(m), 2818(m), 2625(w), 2303(w), 2215(w), 2012(w), 1906(w), 1823(w), 1677(w), 1585(m), 1483(w), 1435(s), 1338(w), 1315(w), 1185(w), 1163(w), 1110(s, ν(CF)), 1023(s), 995(m), 926(w), 883(m, ϑ CH_2F), 846(w), 785(w), 752(m), 739(s), 719(s, ν(CF)), 681(s), 614(w), 530(s) cm^{-1}. Elemental analysis: Calcd. for $C_{19}H_{17}FIP$: C 54.05 H 4.06, found: C 53.86 H 4.12 %. HRMS-FAB (m/z) [M+]: Calcd. for $C_{19}H_{17}FP$: 295.1052, found: 295.1038. Mp.: 170 °C (Dec.).

Single Crystal X-Ray Diffraction Studies

Single crystals of compound **13** (X = I), suitable for X-ray diffraction, were obtained by slow evaporation of a solution in acetonitrile. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71073 Å).

Data collection and data reduction were performed with the CrysAlisPro software.[23] Absorption correction using the multiscan method[24] was applied. The structures were solved with SHELXS-97,[25] refined with SHELXL-97[25] and finally checked using PLATON.[26] Details for data collection and structure refinement are summarized in the supplementary information.

CCDC-1892768 contains supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

We are thankful to F-Select GmbH for a generous donation of CH_2FI. We thank Prof. Dr. T. M. Klapötke for the generous allocation of diffractometer time and for his continuous support. We thank Thomas Schnappinger for the help with the DFT calculations.

Keywords: fluoromethylation • fluoroiodomethane • synthesis • phosphonium salt • crystal structure

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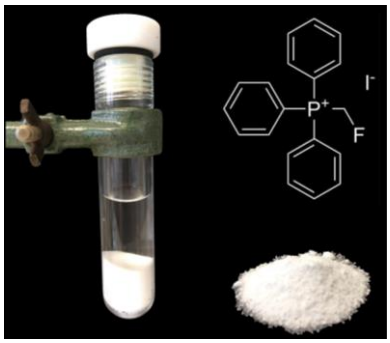
10.1002/ejic.201900165

COMMUNICATION

We present the first example of an X-ray crystal structure analysis of an fluoromethylphosphonium salt. The fluoromethylating agent has been obtained in a simple clean and high yield synthesis making it available in a large scale.



Key Topic*

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Synthesis and properties of the fluoromethylating agent – (fluoromethyl)triphenylphosphonium iodide