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New Method of Preparation of Fluoro compounds via Utilisation of Ammonium and Phosphonium Perfluorocyclobutane Ylides as Fluorination Reagents

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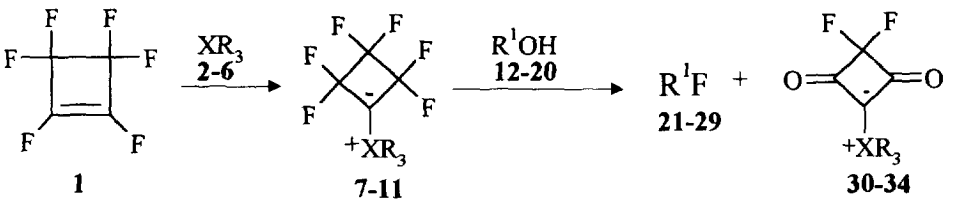
Abstract: Ammonium- and phosphoniumperfluorocyclobutane ylides (**7-11**), easily prepared from perfluorocyclobutene (**1**) and tertiary amines (**2-4**) or phosphines (**5,6**), smoothly react with primary or secondary alcohols (**12-18**) and carboxylic acids (**19,20**) with formation of alkyl fluorides (**21-26**) or acyl fluorides (**27,28**), respectively. A mechanism for the reaction is proposed.

The introduction of a fluorine atom into organic compounds often alters their chemical and biological activity profoundly, due to pronounced changes in the electron distribution and increased lipophilicity. This has stimulated considerable interest in the development of convenient methods for the formation of carbon-fluorine bonds because, unfortunately, most typical reactions suitable for the formation of carbon-halogen bonds cannot be applied. Theoretically, methods that allow the replacement of an OH group in alcohols and carboxylic acids by a fluorine atom under mild conditions, offer one of the most versatile entries to selectively fluorinated molecules. In praxi, however, either highly toxic reagents like SF_4 and dialkylaminosulfur trifluoride (DAST) or rather unstable 2-chloro-1,1,2-trifluorotriethylamine[1,2] or 1,1,2,3,3,3-hexafluoropropyldiethylamine (PPDA)[3-6] [(Yaro- venko or Ishikava reagents, respectively, often referred to as Fluoroalkyl Amino Reagents (FAR)] have to be used for this conversion. FAR have the additional disadvantage that side products formed from reagents are often difficult to separate from products. Recently two new methods using either α-fluoroenamines[7] or the combination of n-perfluorobutanesulfonyl fluoride / diazabicycloundecene have been reported.[8]

We wish to report a new, one step method for the preparation of monofluorocompounds via replacement of hydroxyl groups by fluorine in alcohols or carboxylic acids by their interaction with ammonium- or phosphonium perfluorocyclobutane ylides.

Perfluorocyclobutene is known to react easily with tertiary amines or phosphines giving not substitution products, but stable ammonium or phosphonium hexafluorocyclobutane ylides.[9-11] Their structure and some reactions have been reported in the literature.[9,11] For instance, the interaction of trialkylammoniumhexafluorocyclobutane ylides **7-9** with water gives the 1,4-dioxo-ylides and with ethanol in the presence of picric acid leads to the substitution of one fluorine atom and formation of 2-ethoxytetrafluorocyclobutenetetra-

ethylammonium picrate.[10] We have found that ylides **7-11** react smoothly under neutral conditions with alcohols or carboxylic acids with replacement of the hydroxyl group by a fluorine atom.



1 **7-11** **30-34**

XR_3 = $N(Me)_3$ (**2** ,**7** and **30**), $N(Et)_3$ (**3** ,**8** and **31**), $N(Bu)_3$ (**4, 9** and **32**), $P(NEt_2)_3$ (**5, 10** and **33**), PPh_3 (**6, 11** and **34**).

R^1 = CH_3 (**12** and **21**), CH_2=CH-CH_2 (**13** and **22**), n-C_8H_{17} (**14** and **23**), $PhCH_2$ (**15** and **24**), $PhCH_2CH_2CH_2$ (**16** and **25**), i-C_4H_9 (**17** and **26**), Ph(CH)COOEt (**18** and **27**), PhCO (**19** and **28**), C_6F_5CO (**20** and **29**).

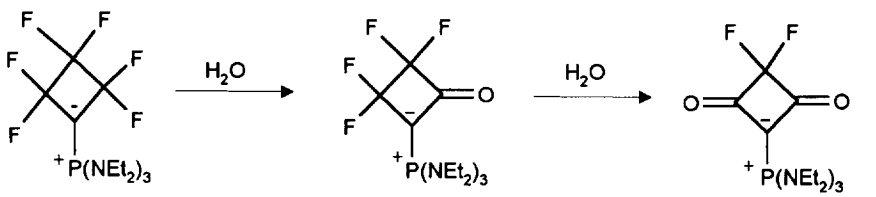
The reaction with primary or secondary alcohols proceeds in high or moderate yields with little side reactions such as olefin formation (Table 1). Best results were achieved with alcohols like methanol, allylalcohol or benzylalcohol which produce stable carbocations without the possibility of olefin formation via elimination of H_2O.

Table 1. Fluorination of Alcohols and Acids with Ammonium and Phosphonium Ylides (**7-11**).

	Organic substrate	Ylide N_o	Reaction conditions Time (h)	Solvent	Product N_o	Yield (%)
12	CH_3OH	8	3*	--	21	76**
		10	2.5*	--		81**
13	CH_2=CH-CH_2OH	10	3*	--	22	71
14	$CH_3(CH_2)_6CH_2OH$	8	5	THF	23	55
		10	5	THF		62
15	$PhCH_2OH$	7	4	CH_2Cl_2	24	39
		8	4	CH_2Cl_2		55
		9	4	CH_2Cl_2		61
		10	4	CH_2Cl_2		76
16	$C_6H_5CH_2CH_2CH_2OH$	10	4*	--	25	62
17	(±) $CH_3CH(OH)CH_2CH_3$	8	3	--	26	65**
		10	2.5	--		68**
18	(±) $C_6H_5CH(OH)COOEt$	10	3	--	27	71**
19	C_6H_5COOH	8	3	THF	28	89
		11	4	THF		67
20	C_6F_5COOH	10	4	CH_2Cl_2	29	91
		11	4	THF		62

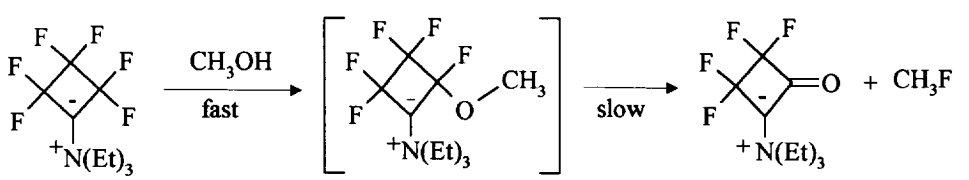
* Reaction under pressure. **Yield determined by ^{19}F NMR or GLC.

For comparison, the reaction of benzylalcohol with Yarovenko or Ishikava reagent gave 40 and 60 % benzylfluoride, respectively.[12,3] The yield of fluorinated products increased with the bulkiness of the XR_3 substituent (compounds **7-11**) and was best for P-ylide **10**. Cyclohexanol, however, gave only 12 % of monofluorocyclohexane with predominant formation of cyclohexene. Weak fluorination activity towards alcohols was observed for ylide **11** derived from triphenylphosphine. All reactions can be carried out by slightly heating the reactants in standard glass apparatus, by solvent free procedures or in common organic solvents such as dichloromethane, tetrahydrofuran or diethyl ether. Reagents are unreactive to most functional groups such as carbon-carbon double bond, ketones, aldehydes, esters, nitriles and can therefore be used for fluorination of polyfunctional compounds. Previously described compounds **7-9, 11**[9-11] and the new ylide **10** are white or pale yellow, moisture-sensitive solids which are stable for a long time in dry atmosphere. The ^1H NMR spectrum of **10** at ambient temperature shows two signals of C_2H_5-groups and the ^{19}F NMR spectrum shows two broad singlets (2:1) at -87.3 and -124.9 ppm, respectively, probably due to rapid conformational changes in the ring. The ^{19}F NMR spectrum of **10** at -50 °C, however, shows two narrow multiplets with symmetrical spin-coupling patterns, of which the coupling constants could not be determined exactly. These data are in good agreement with NMR data obtained for **8** and **11**.[10,11] Hydrolysis of **10** can be carried out sequentially to give monooxo- **35** and dioxobetaines **33** (the latter one was isolated and characterized). Formation of the same products was observed by ^{19}F NMR during the reaction of **10** with alcohols or carboxylic acids.



10 **35** **33**

The reaction of ylides **8** and **10** with alcohols or acids, after work up, gave solid dioxobetaines **31** and **33** with m.p. 92 °C and 167 °C, respectively, from which most fluorinated products could easily be separated. The mechanism proposed for the reaction includes fast displacement of one F-atom in the betaine moiety by the alkoxy group, followed by a slow migration (internal or external) of the fluoride anion to the carbon (S_NI, S_N1 or S_N2 mechanism) with alkyl- or acyl fluoride elimination .



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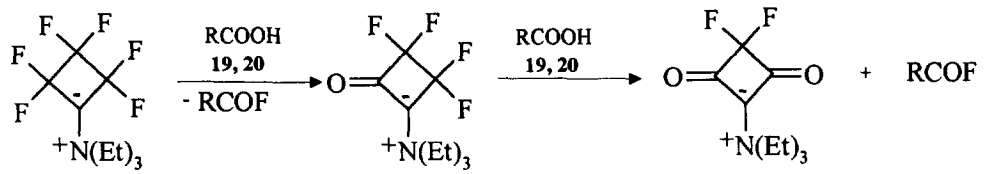
In the case of the more easily fluorinated carboxylic acids the intermediate **36** has still sufficient fluorination power and only 0.5 mol of the ylide is required for each mol of acid.



36 **31** **28, 29**

EXPERIMENTAL SECTION.

Commercially available chemicals were of analytical grade and used without purification.

The reaction products were analyzed by GLC on a Hewlett Packard 5890 Series 2 Chromatograph using a 10 m 0.53 mm column HP-1 (dimethylpolysiloxane). NMR spectra were recorded on an AMX 300 spectrometer (^{19}F: 282.1 MHz, ^{1}H 299.8 MHz, ^{31}P 121.4 MHz). A positive chemical shift denotes a resonance occurring downfield from the external standard CCl_3F and internal TMS. All reactions were carried out in N_2 atmosphere. Perfluorocyclobutene[13], tris(diethylamino)phosphine[14] and ylides **7**, **8**, **9** and **11**[9-11] were prepared according to literature methods.

Tris(diethylamino)phosphonium-2,2,3,3,4,4-hexafluorocyclobutane ylide (10)

To a solution of 24.7 g (0.1 mol) tris(diethylamino)phosphine in 50 ml diethyl ether 16.2 g (0.1 mol) perfluorocyclobutene was added at -40 °C. The reaction mixture was stirred for 1 h at -30 °C and 2 h at 0 °C. After evaporation of the solvent 39.3 g (96 %) of a white hygroscopic solid, m.p. 52-54 °C, was obtained. For analysis the compound was recrystallized twice from diethyl ether at -20 °C. Anal. Calcd. for $C_{16}H_{30}F_6N_3P$: F, 27.87. Found: F, 29.12. ^{1}H NMR (CD_2Cl_2) δ: 1.15 (t, 3H, $^{3}J_{H\text{-}H}$=7 Hz, CH_3), 3.14 (qd, 2H, $^{3}J_{P\text{-}H}$=11 Hz, CH_2). ^{19}F NMR (CD_2Cl_2) δ: -87.3 (bs, 4F), -124.9 (bs, 2F) ppm. ^{31}P NMR δ: 46.8 (bs) ppm.

2-Oxo-3,3,4,4-tetrafluoro-tris(diethylaminophosphonium) betaine (35)

To a solution of 0.01 mol betaine in 10 ml CH_2Cl_2 0.18 g (0.01 mol) of water was added. After 1 h stirring the solvent was removed in vacuo to give a viscous oil containing, according to ^{19}F NMR, 90 % of compound **35** and 10 % of compound **33**. ^{19}F NMR ($CDCl_3$) δ: - 99.9 (dm, 2F), -122.6 (dm, 2F) ppm.

2,4-Dioxo-3,3-difluoro-tris(diethylaminophosphonium) betaine (33)

To a solution of 0.01 mol of compound **10** in 20 ml THF 0.9 g (0.05 mol) of water was added. The reaction mixture was stirred 2 h at ambient temperature and solvent and excess of water were removed in vacuo. The residue was recrystallized from hexane. Yield 98 %. M.p. 96-97 °C. Anal. Calcd. for $C_{16}H_{30}F_2N_3O_2P$: F, 10.41. Found: F, 10.10. ^{1}H NMR ($CDCl_3$) δ: 1.18 (t, $^{3}J_{H\text{-}H}$=7 Hz, 3H), 3.16 (dt, 2H, $^{3}J_{P\text{-}H}$=11,5 Hz) ppm. ^{19}F NMR δ: -120.7 (d, $J_{P\text{-}F}$=22 Hz) ppm. ^{31}P NMR δ: 35.1 (t) ppm. ^{13}C NMR δ: 13.28, 39.16, 108.0 (dt, $^{1}J_{P\text{-}C}$=146 Hz, $^{3}J_{P\text{-}C}$=21 Hz, CP); 127.7 (td, $^{1}J_{C\text{-}F}$=299 Hz, $^{3}J_{P\text{-}C}$=74 Hz, CF_2), 183.8 (dt, CO) ppm.

Fluorination of alcohols (reaction under pressure).

0.5 Mol of betaines **7-10** and 0.3 mol of alcohol (Table 1) were placed in a glass pressure-vessel and heated at 60 °C. The reaction mixture was cooled and volatile product was condensed into a cold trap. For further purifiction the product can be distilled at low temperature.

Methyl fluoride (21), b.p. -78 °C. ^{19}F NMR ($CDCl_3$) δ: -264 (q) ppm (lit[15]).

1-Fluoropropene (22), b.p. -3 °C (lit[15]). ^{19}F NMR ($CDCl_3$) δ: -216.3 (tm, $^2J_{F-H}$=48 Hz) ppm.

2-Fluorobutane (26), b.p. 24 °C. ^{19}F NMR ($CDCl_3$) δ: -173.8 (m) ppm (lit[16]).

Fluorination of alcohols and carboxylic acids.

A solution of 0.1 mol of betaines **7-11** was placed in a three-necked flask equipped with condenser and thermometer, 0.06 mol of alcohol or 0.15 mol carboxylic acid was added over a 30 min. period (exothermic reaction). The reaction mixture was stirred for 2-6 h at 50°C, and both the solvent and product were transferred in vacuo to a cold trap. For further purification the mixture can be distilled at atmospheric pressure or in vacuo. For isolation of alkylfluorides with high boiling points the reaction mixture can be diluted with diethyl ether, washed with water and dried with $MgSO_4$. The product can then be isolated by standard work up procedures.

1-Fluorooctane (23), b.p. 143 °C (lit[3]). ^1H NMR($CDCl_3$) δ: 2.0 (m, 2H), 2.74 (t, 2H), 4.45 (dt, 2H), 7.10-7.30 (m, 5H) ppm. ^{19}F NMR δ: -220.6 (tt, $^2J_{F-H}$=45 Hz, $^3J_{F-H}$=25 Hz) ppm.

Benzylfluoride (24), b.p. 60 °C / 60 mbar (lit[3]). ^{19}F NMR δ: -207.2 (t, $^2J_{F-H}$=48 Hz) ppm.

1-Fluoro-3-phenylpropane (25), b.p. 81 °C / 60 mbar. ^1H NMR ($CDCl_3$) δ: 2.0 (m, 2H), 2.74 (t, 2H), 4.45 (dt, 2H), 7.10-7.30 (m, 5H) ppm. ^{19}F NMR ($CDCl_3$) δ: -220.6 (tt, $^2J_{F-H}$=45 Hz, $^3J_{F-H}$=25 Hz) (lit[8]).

2-Fluorophenylethyl acetate (27), ^1H NMR ($CDCl_3$) δ: 1.2 (t, 3H, CH_3), 4.2 (q, 2H, CH_2), 5.78 (d, 1H), 7.35-7.50 (m, 5H) ppm.[6] ^{19}F NMR ($CDCl_3$) δ: -180.4 (d, $^2J_{F-H}$=50 Hz).

Benzoyl fluoride (28), b.p. 159-161°C. ^{19}F NMR δ: 17.6 ppm.

Pentafluorobenzoyl fluoride (29), b.p. 50-52 °C / 20 mbar, ^{19}F NMR ($CDCl_3$) d: 46.3 (COF) ppm.[17]

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