Convenient Procedures for the Preparation of Lipophilic Quaternary Onium Fluorides, Hydrogendifluorides and Dihydrogentrifluorides via Ion Exchange in Two-Phase Systems

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A series of lipophilic quaternary onium fluorides **2**, hydrogendifluorides **3**, and dihydrogentrifluorides **4** are easily synthesized in almost quantitative yields from the corresponding quaternary hydrogen sulfates by exchange with the appropriate anion in an organic aqueous two-phase system; alternatively quaternary salts **4** can be prepared from onium chlorides **5** or bromides **6** under the same conditions.

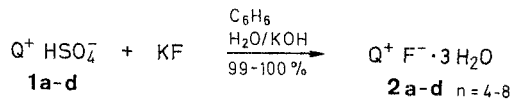
The increasing importance of tetraalkylammonium fluorides **2** as organic-soluble sources of fluoride ions for various purposes in synthetic chemistry is well known.[1-3] In particular tetrabutylammonium fluoride **(2a)** has found widespread use as promotor of reactions involving organosilyl derivatives,[1,2] and of a number of elimination, condensation and fluorination reactions.[1,3] Among lipophilic onium fluorides **2**, only the tetrabutyl derivative **2a** is commercially available as trihydrate compound or supported on silica gel,[4] but its cost is relatively high.

The main methods of synthesis of salts **2**, known in literature, are:[3]

- neutralization of an aqueous solution of the quaternary hydroxides with dilute hydrofluoric acid;
- metathesis $Br^- \rightarrow F^-$ through protracted ion-exchange chromatography; and
- treatment of quaternary bromides with silver fluoride in aqueous solution.[5]

All these methods work in the case of onium salts substantially soluble in water such as the tetrabutyl derivative **2a**, but their extention to more lipophilic ones is not straightforward.

We have found that lipophilic tetraalkylammonium fluorides **2** can be easily prepared by preparative ion-pair extraction from the corresponding hydrogen sulfates[7] **1a–d** in a benzene/saturated aqueous potassium fluoride two-phase system (Scheme **A**).



1, 2	Q+	1, 2	Q+
a	$(n\text{-}C_4H_9)_4N^+$	**e**	$(n\text{-}C_4H_9)_4P^+$
b	$(n\text{-}C_6H_{13})_4N^+$	**f**	$n\text{-}C_{16}H_{33}P^+(C_4H_9\text{-}n)_3$
c	$(n\text{-}C_7H_{15})_4N^+$	**g**	$(C_6H_5)_4P^+$
d	$(n\text{-}C_8H_{17})_4N^+$		

Scheme **A**

The exchange was performed by stirring at room temperature for 1 h a heterogeneous mixture of a benzene solution or a suspension of quaternary hydrogen sulfates **1a–d** (1 mol) and a saturated aqueous solution of potassium fluoride (30 mol) and potassium hydroxide (1.1 mol). In the case of the less lipophilic tetrabutyl derivative **1a**, the exchange was accomplished without organic solvent, and the ammonium fluoride **2a** was extracted from the reaction mixture with acetonitrile. Evaporation of the organic solvent afforded the quaternary ammonium fluorides **2a–d** as trihydrate compounds with a purity $\geq 98\%$ in almost quantitative yields (Table 1).

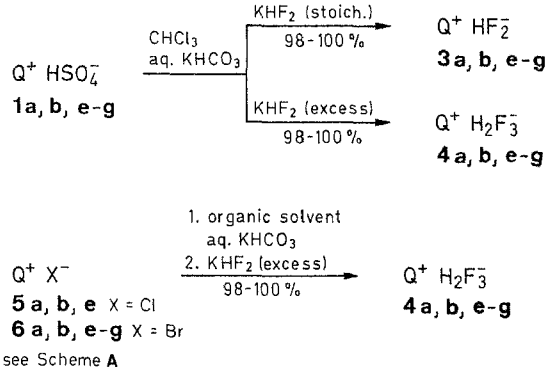
Table 1. Tetraalkylammonium Fluorides **2a–d** Prepared

Product[a]	Yield (%)	mp (°C)	Molecular Formula[b,c] or Lit. mp (°C)
2a	100	61–63	59–62[1]
2b	100	pasty wax	$C_{24}H_{58}FNO_3$ (427.8)
2c	99	oil	$C_{28}H_{66}FNO_3$ (484.0)
2d	100	oil	$C_{32}H_{74}FNO_3$ (540.0)

[a] Isolated as trihydrate salts (Karl-Fischer analysis).
[b] Satisfactory microanalyses obtained: C ±0.42, H ±0.21, N ±0.23.
[c] Fluoride ion was determined by direct potentiometric titration and ^{19}F-NMR analysis (see text).

The use of tetraphenylphosphonium[11] or tetrabutylammonium[12] hydrogendifluorides **(3g)** and **(3a)** as nucleophilic sources of fluoride ions has recently been claimed. These onium salts were obtained through a tedious anion-exchange resin procedure.[11,12] Here we report a more simple method for the preparation of a series of lipophilic quaternary ammonium or phosphonium hydrogendifluorides **3a, b, e–g** starting from the corresponding hydrogen sulfates **1a, b, e–g** (Scheme **B**).

An organic solution of quaternary hydrogen sulfates **1a, b, e–g** (1 mol) was carefully neutralized by stirring with an aqueous



Scheme **B**

Table 2. Quaternary Onium Hydrogendifluorides **3a, b, e–g** Prepared

Product[a]	Yield (%)	mp (°C)	Molecular Formula[b,c] or Lit. mp (°C)
3a	100	pasty wax	ca. 30[16]
3b	100	oil	$C_{24}H_{53}F_2N$ (393.7)
3e	98	oil	$C_{16}H_{37}F_2P$ (298.5)
3f	99	oil	$C_{28}H_{61}F_2P$ (466.8)
3g	100	143–145	–[d,11]

[a] All these salts were isolated as anhydrous compounds.
[b] Satisfactory microanalyses obtained: C ±0.61, H ±0.20, N ±0.23.
[c] Hydrogendifluoride anion HF_2^- was determined by potentiometric acid/base titration and ^{19}F-NMR analysis (see text).
[d] Melting point not reported.

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solution of potassium hydrogen carbonate (1 mol), and then equilibrated with the stoichiometric amount of potassium hydrogen fluoride, added to the heterogeneous mixture as solid salt. Work-up (see experimental) afforded pure quaternary hydrogendifluorides **3a, b, e–g** in almost quantitative yields (Table 2). The use of the stoichiometric quantity of potassium hydrogen fluoride is crucial for the synthesis of salts **3**: i.e. a mixture of hydrogendifluorides **3** and dihydrogentrifluorides **4** were obtained by working with an excess of the inorganic salt.

Indeed the latter quaternary salts **4** (efficient hydrofluorinating agents towards electrophilic alkynes[6]) can be prepared in quantitative yields by using an excess (50 mol per mol of hydrogen sulfate **1**) (Scheme **B**). Dichloromethane, chloroform or benzene can be used as organic solvents.

Alternatively quaternary salts **4** can be obtained directly from the corresponding commercially available onium chlorides or bromides **5** and **6** under the above conditions (Scheme **B**). A complete anion exchange was reached after two and three equilibrations in the case of chlorides **5** and bromides **6**, respectively, using 50 moles of potassium hydrogen fluoride per mole of starting material in each run (Table 3). Our procedures represent valid alternatives to that recently reported[6] for the synthesis of tetrabutylammonium derivative **4a**, which involves the use of the corresponding fluoride **2a** as starting quaternary onium salt.

Table 3. Quaternary Onium Dihydrogentrifluorides **4a, b, e–g** Prepared

Product[a]	Yield (%)	mp (°C)	Molecular Formula[b,c] or Lit. mp (°C)
4a	100	oil	oil[6]
4b	100	oil	$C_{24}H_{54}F_3N$ (413.8)
4e	100	oil	$C_{16}H_{38}F_3P$ (318.5)
4f	98	oil	$C_{28}H_{62}F_3P$ (486.9)
4g	100	181–183	$C_{24}H_{22}F_3P$ (398.4)

[a] All these salts were isolated as anhydrous compounds.
[b] Satisfactory microanalyses obtained: C ±0.37, H ±0.20, N ±0.16.
[c] Dihydrogentrifluoride anion $H_2F_3^-$ was determined by potentiometric acid/base titration and ^{19}F-NMR analysis (see text).

All quaternary onium fluorides **2**, hydrogendifluorides **3** and dihydrogentrifluorides **4** were characterized by microanalysis, fluoride ion or acid/base titration, and by ^{19}F-NMR analyses.

The fluorides **2** are hygroscopic compounds, unlike the salts **3** and **4**, which are easily obtained as anhydrous non-hygroscopic and stable products. The ^{19}F-NMR spectra of the onium fluorides **2a–d**, hydrogendifluorides **3a, b, e–g**, and dihydrogentrifluorides **4a, b, e–g** show one broad resonance centered at ca. $\delta = -120$, -145, and -160, respectively, in agreement with the values reported in the literature.[6,13,14]

The inorganic salts and solvents were Analar grade commercial products, used without further purification. Quaternary onium chlorides **5** and bromides **6** were purchased from Fluka Chemical Co. Quaternary onium hydrogen sulfates **1** are known compounds, prepared according to a previously reported procedure.[10] Potentiometric titrations were obtained with a Metrohm Titroprocessor E 636 by using AgF or glass and calomel electrodes, the latter isolated with potassium sulfate bridge. Karl Fischer analyses were obtained with a Metrohm Automat E 547.

The ^{19}F-NMR spectra were performed with a Varian XL 300 MHz spectrometer operating at 282.2 MHz, and chemical shifts are referred to $CFCl_3$ as external reference. The samples, typically 0.15 M, were dissolved in CD_2Cl_2

Quaternary Ammonium Fluorides 2a–d; General Procedure:
In a flask equipped with a mechanical stirrer a solution or a suspension of the respective ammonium hydrogen sulfate[10] **1** (50 mmol) in benzene (500 mL) is equilibrated for 1 h at room temperature with a concentrated aqueous solution (150 mL) of KF (87.2 g, 1.5 mol) and KOH (3.1 g, 55 mmol). The organic phase is separated and evaporated at 40–50 °C in vacuum (water-pump), to give onium fluorides $Q^+F^- \cdot nH_2O$ **(2)** as polyhydrate substances ($n = 4–8$) (Karl Fischer analysis). The salts **2** are obtained as trihydrate compounds by azeotropic distillation in vacuum using a benzene/CH_3CN mixture (1:1).[15] Further dehydration causes partial decomposition of the salts **2**.[14] The synthesis of tetrabutylammonium fluoride **2a** is accomplished without organic solvent, by stirring an aqueous solution of starting hydrogen sulfate **1a** (50 mmol, 60 mL) with KF and KOH for 20 min. The fluoride **2a** is extracted with CH_3CN (3 × 50 mL) from the mixture. Work-up as described above gives the pure quaternary fluoride **2a** as trihydrate salt (Karl Fischer analysis). The purity of fluorides **2a–d**, so obtained, is ≥ 98% by potentiometric titration of fluoride ion with $La(NO_3)_3$ in a CH_3OH/H_2O mixture (3:2). Their physical properties and yields are reported in Table 1. Chlorinated solvents, such as CH_2Cl_2 or $CHCl_3$, should be avoided because they react in part with Q^+F^- during the work-up giving chlorides **5** in small amounts.

Quaternary Onium Hydrogendifluorides 3a, b, e–g; General Procedure:
In a polymethylpentene flask fitted with mechanical stirrer a solution of quaternary onium hydrogen sulfate **1**[10] (100 mmol) in $CHCl_3$ (500 mL) is neutralized by stirring for 10 min at room temperature with an aqueous solution (25 mL) of $KHCO_3$ (10 g, 100 mmol). Then KHF_2 (7.8 g, 100 mmol) is added as solid salt, and the mixture is stirred for 1 h. In the case of tetraphenylphosphonium derivative **1g** CH_3CN is used as organic solvent. The organic layer is separated and evaporated under vacuum applying oil-pump towards the end at ca. 60 °C for 4 h, to afford anhydrous quaternary onium hydrogendifluorides **3** together with traces of the corresponding dihydrogentrifluorides **4**. The crude product is dissolved in CH_3CN (100 mL), stirred for 10 min with anhydrous K_2CO_3 (2 g) and filtered. Evaporation of the solvent under vacuum at ca. 60 °C gives pure quaternary onium hydrogendifluorides **3a, b, e–g** in almost quantitative yields (≥ 98%). They are characterized by potentiometric acid/base titration of HF_2^-, ^{19}F-NMR, and microanalyses (Table 2).

Quaternary Onium Dihydrogentrifluorides 4a, b, e–g; General Procedure:

Method A *(starting from quaternary hydrogen sulfates* **1a, b, e–g***)*: The synthesis of quaternary onium dihydrogentrifluorides **4a, b, e–g** is carried out as described above for the preparation of hydrogendifluorides using 50 moles of KHF_2 per mole of starting salt **1**. After equilibration, the organic layer is separated, and evaporated under vacuum applying oil-pump towards the end at ca. 60 °C for 4 h, to give anhydrous quaternary dihydrogentrifluorides **4a, b, e–g** in quantitative yields with a purity ≥ 98% (by potentiometric acid/base titration of $H_2F_3^-$, ^{19}F-NMR and microanalysis) (Table 3).

Method B *(starting from quaternary chlorides* **5a, b, e** *or bromides* **6a, b, e–g***)*: In a polymethylpentene flask, an organic solution (CH_2Cl_2, $CHCl_3$ or benzene) (50 mL) of the respective chloride **5** or bromide **6** (10 mmol) is equilibrated at room temperature for 30 min with an aqueous solution (100 mL) of KHF_2 (39.1 g, 500 mmol) two and three times in the case of **5** and **6**, respectively. Work-up, as described in Method A affords onium dihydrogentrifluorides **4a, b, e–g** in similar yields.

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(1) Ogilvie, K.K., Beaucage, S.L., Gillen, M.F. *Tetrahedron Lett.* **1978**, *19*, 3203.
Ogilvie, K.K., Beaucage, S.L., Gillen, M.F., Entwistle, D.W. *Nucl. Acids Res.* **1979**, *6*, 2261.
Nayori, R., Yokoyama, K., Sakata, J., Kuwajima, I., Nakamura, E., Shimizu, M. *J. Am. Chem. Soc.* **1977**, *99*, 1265.
Just, G., Tsantriozos, Y.S., Ugolini, A. *Can. J. Chem.* **1981**, *59*, 2981.
Matsumoto, K. *Angew. Chem.* **1981**, *93*, 803; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 770.
Hough, L., Penglis, A.A.E., Richardson, A.C. *Can. J. Chem.* **1981**, *59*, 396.
McCullough, K.J. *Tetrahedron Lett.* **1982**, *23*, 2223.
Himeshima, Y., Sonoda, T., Kobayashi, H. *Chem. Lett.* **1983**, 1211.
Guindon, Y., Fortin,. R., Yoakim, C., Gillard, J.W. *Tetrahedron Lett.* **1984**, *25*, 4717.
Collington, E.W., Finch, H., Smith, I.J. *Tetrahedron Lett.* **1985**, *26*, 681.
Haas, A., Lieb, M. *Chimia* **1985**, *39*, 134.
(2) Kuwajima, I., Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181.
Lalonde, M., Chan, T.H. *Synthesis* **1985**, 817, and references therein.
(3) Clark, J.H. *Chem. Rev.* **1980**, *80*, 429, and references therein.
(4) Clark, J.H. *J. Chem. Soc. Chem. Commun.* **1978**, 789.
(5) Recently the tetrabutylammonium fluoride **(2a)** was prepared from the corresponding tetrafluoroborate by exchange with F^- in aqueous solution.[6]
(6) Cousseau, J., Albert, P. *Bull. Soc. Chim. Fr.* **1986**, 910.
(7) Lipophilic tetraalkylammonium hydrogen sulfates **1** can be easily obtained in large quantities according to previously reported procedures;[8-10] tetrabutyl and tetrahexyl derivatives **1a, c** are commercially available products.
(8) Brändström, A., in: *Preparative Ion Pair Extraction: An Introduction to Theory and Practice*. Apotekarsocieten, Box 1136, S-11181, Stockholm, 1974, p. 141.
(9) Dehmlow, E.V., Vehre, B., Broda, W. *Synthesis* **1985**, 508.
(10) De Giorgi, M., Landini, D., Maia, A., Penso, M. *Synth. Commun.* **1987**, *17*, 521.
(11) Brown, S.J., Clark, J.H. *J. Chem. Soc. Chem. Commun.* **1985**, 672.
Brown, S.J., Clark, J.H. *J. Fluorine Chem.* **1985**, *30*, 251.
(12) Bosch, P., Camps, F., Chamorro, E., Gasol, V., Guerrero, A. *Tetrahedron Lett.* **1987**, *28*, 4733.
(13) Clark, J.H., Goordman, E.M., Smith, D.K., Brown, S.J., Miller, J.M. *J. Chem. Soc. Chem. Commun.* **1986**, 657.
(14) Sharma, R.K., Fry, J.L. *J. Org. Chem.* **1983**, *48*, 2112.
Cox, D.P., Terpinski, J., Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216.
(15) Corey, E.J., Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(16) Martin, J.S., Fujiwara, F.Y. *Can. J. Chem.* **1971**, *49*, 3071.

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