Difluoromethyltrialkylammonium Salts—Their Expeditious Synthesis from Chlorodifluoromethane and Tertiary Amines in the Presence of Concentrated Aqueous Sodium Hydroxide. The Catalytic Process

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$$\underset{\mathbf{1}}{R^1R^2R^3N} + HCClF_2 \xrightarrow[\text{NaX or KX}]{\text{50\% aq NaOH, THF}} \underset{\mathbf{2\text{-}5}}{R^1R^2R^3\overset{\oplus}{N}CHF_2\overset{\ominus}{X}}$$

X = Cl, I, NO$_3$, SCN

We found that difluorocarbene generated from chlorodifluoromethane with 50% aqueous sodium hydroxide reacts with lipophilic tertiary amines **1a**−**g** giving difluoromethyltrialkylammonium chlorides **2a**−**g** in high yields. Similarly, difluoromethyltrialkylammonium iodides **3h**−**l**, nitrates **4h**−**k**, or isothiocyanates **5i**,**j** were synthesized from hydrophilic tertiary amines **1h**−**l** and the corresponding sodium or potassium salts. The process is catalytic with respect to the base used.

Reactions of dihalocarbenes with amines yield ammonium ylides, which transform further giving products.[1] Dichloro- or dibromocarbene, generated from the corresponding haloforms with concentrated aqueous alkali metal hydroxides and a quaternary ammonium salt (quat) as a catalyst (phase-transfer catalysis, PTC[2]), react with primary or secondary amines affording isonitriles[3] or *N*,*N*-dialkylformamides[4] respectively, often in synthetically acceptable yields. On the other hand, reactions of these carbenes with tertiary amines usually give complex products mixtures in low yields even when intermediary ylides are prone to sigmatropic rearrangements.[1] Therefore, these processes are devoid of synthetic value.

A convenient source of difluorocarbene is chlorodifluoromethane (Freon R-22[5]). We noticed that the reaction of Freon R-22 with tertiary amines **1** carried out in the presence of 50% aqueous sodium hydroxide in THF, without any added catalyst, gave difluoromethyltrialkylammonium chlorides **2**.

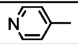
SCHEME 1

$$\underset{\mathbf{1}}{R^1R^2R^3N} + HCClF_2 \xrightarrow[\text{rt, 2-12 h}]{\text{50\% aq NaOH, THF}} \underset{\mathbf{2}}{R^1R^2R^3\overset{\oplus}{N}CHF_2\overset{\ominus}{Cl}}$$

SCHEME 2

$$\underset{\mathbf{1}}{R^1R^2R^3N} + HCClF_2 \xrightarrow[\text{0-5°C, 2-5.5 h}]{\text{50\% aq NaOH, THF, NaX or KX}} \underset{\mathbf{2\text{-}5}}{R^1R^2R^3\overset{\oplus}{N}CHF_2\overset{\ominus}{X}}$$

TABLE 1. Difluoromethyltrialkylammonium Chlorides 2 Prepared

Entry		**1, 2**			**2**	
		R^1	R^2	R^3	time [h]	yield [%]
1	**a**	C$_{10}$H$_{21}$	(CH$_2$)$_5$		3.5	96
2	**b**	C$_{10}$H$_{21}$	CH$_3$	C$_2$H$_5$	2	95
3	**c**	C$_4$H$_9$	C$_4$H$_9$	C$_6$H$_5$CH$_2$CH$_2$	12	93
4	**d**	C$_8$H$_{17}$	C$_8$H$_{17}$	C$_8$H$_{17}$	3.5	92
5	**e**	C$_4$H$_9$	C$_4$H$_9$	C$_4$H$_9$	3	92
6	**f**	C$_{16}$H$_{33}$	CH$_3$	CH$_3$	4	81
7	**g**	C$_3$H$_7$	C$_3$H$_7$	C$_3$H$_7$	3	59
8	**h**	C$_4$H$_9$	C$_2$H$_5$	CH$_3$	4	5[a]
9	**i**	C$_2$H$_5$	C$_2$H$_5$	C$_2$H$_5$	3.5	4[a]
10	**j**	CH$_3$	(CH$_2$)$_5$		3	1[a]
11	**k**	CH$_3$	CH$_3$	(CH$_2$)$_6$	4	0
12	**l**		CH$_3$	CH$_3$	2	0

[a] Products **2h**−**j** were contaminated with amines **1h**−**j** and unidentified impurities.

Described methods used for the preparation of these salts are impractical. For reaction with tertiary amines, fluoroorganic derivatives of tin,[6] zinc, and cadmium or bismuth,[7] often in combination with boron or aluminum halides, were used. Alternatively, the reactions of trimethylamine with dibromodifluoromethane and zinc or magnesium,[8] or quaternization of not easily available (difluoromethyl)dimethylamine,[8] were used for that purpose. Recently, difluoromethyl ammonium salts were obtained from *S*-(difluoromethyl)diarylsulfonium tetrafluoroborate and tertiary amines.[9]

The process we elaborated is very simple. It consists of bubbling in gaseous Freon R-22 through the stirred mixture of amine **1** and the base in THF. After decantation of the organic phase from semisolid inorganic products, and the drying and evaporation of the solvent, the crystalline analytically pure salts **2** were obtained (Scheme 1and Table 1).

According to data in Table 1 (entries 1−6), only lipophilic amines **1a**−**f** gave salts **2a**−**f** in a yield exceeding 80%. In the case of amine **1g** of lower molecular weight, the yield of salt **2g** decreased (Table 1, entry 7) and became negligible when hydrophilic amines **1h**−**l** were used (Table 1, entries 8−12). In these cases, large amounts of unreacted amines **1h**−**l** were

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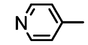
TABLE 2. Difluoromethyltrialkylammonium Salts 2−5 Prepared

Entry		**1-5**			salt **2-5**[a]			
					2[b] X=Cl	**3** X=I	**4** X=NO$_3$	**5** X=SCN
		R^1	R^2	R^3	yield [%]	yield [%]	yield [%]	yield [%]
1	**h**	C$_4$H$_9$	C$_2$H$_5$	CH$_3$	5	89	97	-
2	**i**	C$_2$H$_5$	C$_2$H$_5$	C$_2$H$_5$	4	29	87	90
3	**j**	CH$_3$	(CH$_2$)$_5$		1	53	23	85
4	**k**	(CH$_2$)$_6$	CH$_3$	CH$_3$	0	69	93	-
5	**l**		CH$_3$	CH$_3$	0	77	-	-

[a] Reactions were carried out for 2−5.5 h. [b] Reaction was carried out without added salt (see Scheme 1 and Table 1).

TABLE 3. Yields of 2e versus Amount of Sodium Hydroxide

entry[a]	NaOH/**1e** (mol/mol)	yield **2e** (%)
1	0.1	32
2	0.5	75
3	3	88
4	6	92

[a] Reactions were carried out for 3 h.

present in the reaction mixtures. These observations indicate that hydrophilic amines **1h**−**l** cannot enter into the organic phase (they reside in the water phase or at the interphase of two immiscible phases) and form ylides or subsequently salts **2** (except for a small percent of **2h**−**j**); hence, difluorocarbene undergoes hydrolysis.

Therefore, insufficient lipophilicity of amines **1h**−**l** preventing the formation of the salts was compensated by using iodides, nitrates, or thiocyanates as counteranions, which are more lipophilic than the chloride anion.[10] Indeed, while the reaction of Freon R-22 with triethylamine (**1i**) and concentrated aqueous sodium hydroxide gave **2i** in 4% yield, the addition to the reaction excess of either sodium iodide, sodium nitrate, or potassium thiocyanate afforded **3i**, **4i**, or **5i** in 29, 87, or 90% yield, respectively (Table 2, entry 2).

A similar trend was observed in the case of other hydrophilic tertiary amines **1h**,**j**−**l**, which gave the corresponding iodides **3**, nitrates **4**, and thiocyanates **5** (Table 2, entries 1 and 3−5). Data collated in Tables 1 and 2 clearly demonstrate that a high yield of salts **2**−**5** is assured only in those cases when either lipophilic amine or counteranion is applied.

The reaction studied exhibits another interesting feature, namely, a catalytic nature with respect to sodium hydroxide. Experiments with Freon R-22, amine **1e**, and different quantities of sodium hydroxide revealed that when the ratio of NaOH/**1e** (mol/ mol) = 0.1 or 0.5, the yield of salt **2e** was higher than the amount of base used (Table 3, entries 1 and 2).

This means that the base used for the generation of difluorocarbene is regenerated in the process. To clarify the situation, we carried out a reaction of **1e** (1 equiv) with Freon R-22 and sodium hydride (0.5 or 3.0 equiv) in THF. In either condition, the yield of **2e** did not exceed 3%. Therefore, it seems that water is needed in the system, and all these experimental data allow us to present mechanistic pathways leading to salts **2**−**5**; the case of **2e** is shown in Figures 1 and 2.

Difluorocarbene (generated from Freon R-22 with sodium hydroxide) reacts with the amine, giving ylide **6**, which is protonated with water with formation of salt **7**. The latter can either exchange anion with chloride (or any other lipophilic anion present in the system) affording the salt **2** and hydroxy anion (Figure 1) or acts as a base and deprotonates Freon R-22. This process leads to salt **8** and water, and the salt **8** in turn splits into the product **2** and difluorocarbene (Figure 2). Either of the synthetic pathways may be responsible for the catalytic nature of the reaction.

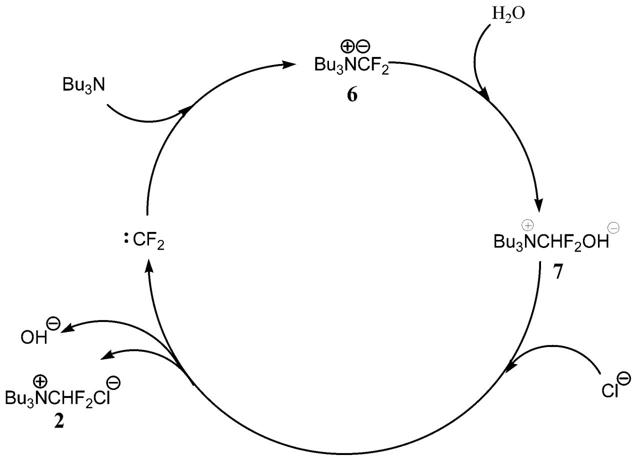


FIGURE 1.

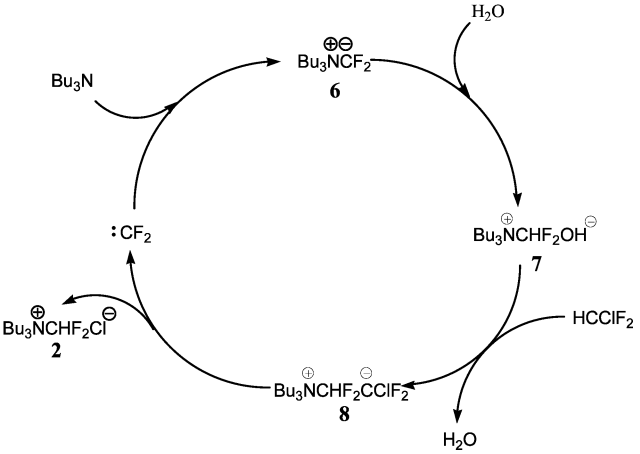


FIGURE 2.

We describe an unprecedented, simple, and high-yield synthesis of difluoromethyltrialkylammonium salts. The crucial point for deciding the success of this process is the lipophilicity of either tertiary amines or counteranion used.

Experimental Section

General Procedure for Preparation of Difluoromethyltrialkylammonium Chlorides 2. Into a three-necked, round-bottomed flask equipped with a reflux condenser, mechanical stirrer, and glass pipe for introducing chlorodifluoromethane, amine **1** (8 mmol), 50% aq NaOH (3.84 g, 2.56 mL, 48 mmol), and THF (20 mL) were placed. The contents of the flask were stirred for ca. 2 min, then chlorodifluoromethane was bubbled through the mixture for 2−12 h, and the progress of the reaction was monitored by GC. The mixture was diluted with CH$_2$Cl$_2$ (50 mL), and the organic phase was decanted from the semisolid inorganic phase, which was stuck to the wall of the flask, and dried over MgSO$_4$. The solvent was evaporated under reduced pressure, giving solid difluromethyltrialkylammonium chlorides **2** (Table 1).

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General Procedure for Preparation of Difluoromethyltrialkylammonium Salts 3−5. The reaction was carried out as described previously starting from amine **1** (8 mmol), 50% aq NaOH (3.84 g, 2.56 mL, 48 mmol), and sodium iodide or sodium nitrate or potassium thiocyanate (24 mmol) and THF (20 mL). The contents of the flask were stirred for ca. 2 min, and then chlorodifluoromethane was bubbled through the mixture at 0−5 °C for 2−5.5 h. The mixture was diluted with CH_2Cl_2 (50 mL), and the organic phase was decanted from the semisolid inorganic phase, which was stuck to the wall of the flask. The solvent was evaporated, the residue was dissolved in CH_2Cl_2 (10 mL) and filtered through a Schott funnel, and the solvent from the filtrate was evaporated, giving solid difluoromethyltrialkylammonium salts **3−5** (Table 2).

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Supporting Information Available: Compound characterization data (^1H NMR, ^{13}C NMR, ^{19}F NMR, and elemental analysis or HRMS of **2a−g**, **3h−l**, **4h−k**, **5i**, and **5j**) and copies of ^1H NMR spectra of **2a−g**, **3h−l**, **4h−k**, **5i**, and **5j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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