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A useful conversion of alcohols to alkyl fluorides

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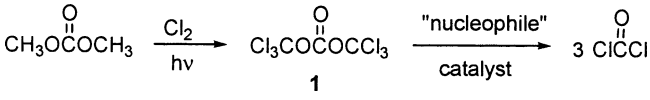
Abstract—A useful conversion of alcohols to alkyl fluorides via their fluoroformates is introduced. The fluoroformates are obtained in nearly quantitative yield from the alcohols by treatment with COF_2 (generated in situ from bis(trichloromethyl) carbonate) in ether with KF as an added acid scavenger. The neat fluoroformates are cleaved to the fluorides by heating at 120–125°C using hexabutylguanidinium fluoride (HBGF) as the catalyst. © 2002 Elsevier Science Ltd. All rights reserved.

While fluorine rarely is found in naturally occurring organic compounds, chemists have synthesized hundreds of thousands of organofluorine compounds because introduction of fluorine into an organic molecule affects its chemical, physical, and biological properties, often with useful consequences.[1,2]

Because alcohols are readily available, an attractive scheme for introducing fluorine into organic compounds is by replacement of hydroxyls. The disadvantages of classic reagents for this conversion (SF_4,[1,3] DAST,[1,3,4] FAR[4]) often include poor yields, dangerous reaction conditions, and difficult reagent manipulations. In the only published route from alcohols to alkyl fluorides involving fluoroformate intermediates,[5] the fluoroformates are heated with BF_3 or pyridine for several hours, conditions which destroy most functionalities.

In the chemistry described here, fluoroformates also are obligatory intermediates, so success depends on their ready availability. In the 1980s, Dang and Olofson converted phosgene by halogen exchange to COF_2, which was bubbled as formed into a solution of the alcohol in CCl_4 using the otherwise inert dried KF as the acid scavenger ($\rightarrow KHF_2\downarrow$) in the acylation step.[6,7] The halide exchange was performed with either NaF in acetonitrile–sulfolane[8] or KF plus 1.1 mol% of 18-crown-6 in acetonitrile. Inclusion of a dry ice condenser as part of the reaction apparatus prevented any $COCl_2$ or COFCl from passing into the alcohol solution.

More recently, an important advance relating to the chemistry herein has been the widespread introduction of bis(trichloromethyl) carbonate (triphosgene, **1**) as a phosgene equivalent for both laboratory and commercial use.[9,10]



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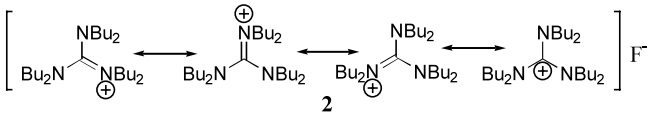
In an obvious but previously untested extension of the above, **1** is the direct source of COF_2 in the laboratory synthesis of alkyl fluorides reported here. **CAUTION**! Although **1** is stable thermally above 100°C,[10] it is easily converted to 3 equiv. of phosgene by treatment with a small amount of most nucleophilic catalysts ('Cl^-', pyridine, Ph_3P, Et_3N, etc.) at 0°C.[10,11] Thus, while triphosgene is much safer and easier to handle than phosgene, all precautions used[11] with phosgene must be taken. Note that benzylic and allylic alcohols react directly with **1** to give the corresponding chlorides.[12]

Hexabutylguanidinium chloride (HBGCl) was introduced as an efficient catalyst for the phosgenation of carboxylic acids by SNPE in the early 1980s.[13] In subsequent collaborations between SNPE and this laboratory, its general value as a 'naked chloride' source was established.[13,14] Unlike $R_4N^+Cl^-$ phase transfer catalysts, HBGCl is stable above 200°C in polar and nonpolar solvents. Unlike crown ethers which sometimes are nearly as active in high temperature processes, HBGCl is very cheap (from Bu_2NH and phosgene in one-pot[13]). In the present study, the value of HBGF (**2**) as a 'naked fluoride' catalyst is first tested.



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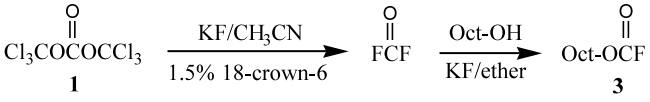
As anticipated,[15] when equimolar solutions of KF and HBGCl in methanol were combined, KCl precipitated. After filtration and rotoevaporation, the concentrate was diluted with 2-propanol, refiltered to remove the remaining KCl, concentrated, and heated at ca. 0.1 mm overnight at 80°C to give HBGF in 97% yield as an orange, hygroscopic wax.

The triphosgene-initiated conversion of alcohols to alkyl fluoroformates was optimized using 1-octanol.



In this process,[16] 18-crown-6 (1.5 mol% versus KF) in CH_3CN was dripped into stirred **1** (2 phosgene equiv. versus 1-octanol) and KF (1.2 equiv. per Cl to be exchanged) in CH_3CN. As it formed, the COF_2 passed into a collector containing octanol, KF, and ether. Rotoevaporation afforded 1-octyl fluoroformate[7b] (**3**) in 100% yield. On a 6 g scale,[16] the distilled yield was 83% and no side products were found an indication of the advantages of using undistilled fluoroformate in the alkyl fluoride forming step.

These conditions were extended to the preparation of the fluoroformates, **4**–**16**, as outlined in Table 1. In these products, the IR C=O stretch at 1830 cm^{-1} for **3**–**10** and 1825 cm^{-1} for **11**–**16** matched reported values for similar compounds.[7,17] The ^1H NMR δs $FCO_2C\underline{H}$- resonances are at 4.2–4.3 for the primary CH's and 4.7–5.0 for the secondary CH multiplets (axial CH of *trans*-**15** at δ 4.6–4.5). In the ^{13}C NMR spectra, the C=O absorbs at δ 145.6–145.9 (**3**–**10**) or δ 145.1–145.6 (**11**–**16**) with J_{13CF} values of 1126–1131 Hz. The $FCO_2\underline{C}H$- δs are at 70.3–74.5 (**3**–**10**) and 78.7–84.0 (**11**–**16**) with J_{COCF} values of 8.5–12 Hz.

The HBGF-catalyzed conversion of alkyl fluoroformates to alkyl fluorides was optimized[18] with **3**. When undistilled **3** was heated with HBGF (7 mol%) at 125°C, 1-fluorooctane[19] (**17**) was isolated in 89% overall distilled yield from 1-octanol. With $Bu_4N^+F^-$ in place of the HBGF, the catalyst decomposed before the reaction was done.

Because 1-fluorohexane[20] (**18**) is more volatile than **17**, more care was taken to avoid evaporative loss. Using the above apparatus, **18** distilled as it formed (91% yield). Less volatile primary alkyl fluorides **19**–**24** were vacuum distilled from the reaction mixture when the process was complete. Data including key NMR values for **17**–**24** are summarized in Table 2. While fluorides **17** and **22** were prepared from the undistilled fluoroformates, the others were made from the distilled reactant. The main side reaction is carbonate formation, typically only 2–7% but greater in the slower process with a hindered reactant (see **22**). The synthesis of 1-chloro-6-fluorohexane (**24**) failed. While the yield of **24** was 57%, both the 1,6-difluoro and 1,6-dichloro products also were found. Thus, at least two kinds of halide exchange are major side reactions under the required conditions.

Table 1. Fluoroformates made from corresponding alcohols

No.	Product FCO_2R R=	Distilled yield (%) (NMR yield[a] (%))	Bp (°C/mm)
3	1-Octyl	83 (100)	57–60/3
4	1-Hexyl	87 (100)	27–29/3
5	3,7-Dimethyl-1-octyl	83 (94)	72–74/1
6	1-(3-Cyclohexylpropyl)-	89 (97)	78–80/2
7	1-(3-Phenylpropyl)-	91 (96)	81–82/0.5
8	2-Hexyl-1-decyl-	(99)	140–142/2.5
9	1-(Undec-10-enyl)-	85 (98)	79.5–83/1
10	6-(-1-Chlorohexyl)-	89	75.5–77/1
11	2-Octyl-	88 (96)	39–42/1
12	2-Decyl-	91 (98)	78–79/2.5
13	2-Dodecyl-	96	98–99/2
14	4-Decyl-	(96)	60–61/1
15	4-*tert*-Butylcyclohexyl-[b]	77 (86)	72–73/2
16	*S*-(+)-2-Octyl-	90	45–48/1.5

[a] Based on analysis of product after rotary evaporation but before distillation. The only contaminant at this point is residual ether.
[b] 33% *cis*, 67% *trans*. More ether (40 versus 10 mL) was used in this synthesis

Secondary alkyl fluorides prepared by the new methodology are listed in Table 3 along with significant NMR data. In the best procedure with undistilled 2-octyl fluoroformate (**11**), the reaction flask was topped by a dry ice condenser instead of a water-cooled condenser. When **11** was syringed onto the dried HBGF (15 mol%) and the resulting mixture stirred at 120°C for 7 h (under dry ice/CH_3CN at –43°C), a mixture of 2-fluorooctane (**25**) (71% yield), di-2-octyl carbonate (accounting for 9% of **11**), 1-octene (3%), and 2-octene (6%) was obtained (^1H NMR analysis, chlorobenzene internal standard), with 11% of **11** unaccounted for. (With 15% $Bu_4N^+F^-$ at 120°C for 6 h, the reaction was only half finished and more carbonate formed). When the above process was used to make the less volatile 2-fluorodecane[21] (**26**) from the fluoroformate **12** (7 h, 15% HBGF, 125°C), a mixture of **26** (75% yield versus 71% for **25**), 1-decene (4%), 2-decene (6%), and di-2-decyl carbonate (from 10% of **12**) was obtained, with 5% unaccounted for.

Methodology including a process for the isolation of pure product was developed for the preparation of the less volatile 2-fluorododecane[22] (**27**) from **13**. After 7 h at 120°C with 15% HBGF (water-cooled condenser), the reaction mixture was diluted with pentane and stirred with silica gel (twice weight of HBGF) to remove the catalyst. After filtration, the mixture in pentane was titrated with Br_2 to convert the alkenes to high boiling products and finally vacuum distilled to isolate pure **27** in 73% yield.

Table 2. Primary alkyl fluorides prepared from the corresponding fluoroformates

No.	Product R-F R=	Mol % HBGF[a] (rxn time (h))	Distilled yield (%) (NMR yield[b] (%))	Overall yield (%) (from alcohol[c] (%))	Bp (°C/mm)	Carbonate yield[d] (%)	^{1}H NMR: FCH-shift (J_{HF} Hz[e]) (J_{CH} Hz[f])	^{13}C NMR: FC-shift (J Hz[e])
17	1-Octyl-	7 (1)	89 (91)	89 (91)	136–137/atm	2	4.42 (48) (7,t)	84.2 (652)
18	1-Hexyl-	7 (1)[g]	91 (92)	79 (92)	92–93/atm	3	4.40 (50) (7.7,t)	84.3 (652)
19	3,7-Dimethyl-1-octyl-	7 (2)	81 (83)	67 (78)	41–42/3	7	4.48 (47) (6,t)	82.8 (650)
20	1-(3-Cyclohexylpropyl)-	7 (2)	88	78 (85)	36–37/1	–[h]	4.42 (48) (6.2,t)	84.6 (654)
21	1-(3-Phenylpropyl)-	7 (2)	85 (87)	77 (84)	45–46/3	6	4.43 (47) (5.8, t)	83.1 (656)
22	2-Hexyl-1-decyl-	15 (3)	85 (86)	84 (85)	118–120/2	10	4.32 (48) (5.2,d)	86.7 (668)
23	1-(Undec-10-enyl)-	7 (2)	83 (87)	71 (81)	67–68/2.5	4	4.43 (49) (6.3,t)	84.2 (652)
24	6-(1-Chlorohexyl)-	7 (1.5)[g]	(57)	–	–	–	4.45 (47) (5,t)	84.0 (654)

[a] Reactions at 125°C unless otherwise specified.
[b] Includes product remaining in still pot after distillation.
[c] The first number is the actual yield using distilled fluoroformate except in the synthesis of **17** and **22** where undistilled fluoroformate was used as the reactant in the second step. The number in parentheses is based on undistilled fluoroformate and includes any product remaining in the still pot.
[d] Amount of fluoroformate converted to carbonate. Excluding the processes yielding **20** and **24**, carbonate yields were determined by NMR analysis of the residue in the still pot. No olefins were found in the product.
[e] All are doublets.
[f] Multiplicity: d = doublet, t = triplet.
[g] Reaction at 120°C.
[h] Still pot not analyzed.

Table 3. Secondary alkyl fluorides prepared from the corresponding fluoroformates

No.	Product R-F R=	Mol % HBGF[a] (rxn time (h))	Isolated yield (%) (NMR yield[b] (%))	Overall yield from alcohol[c] (%)	Olefin yield (%) (carbonate yield (%))[b]	^{1}H NMR: FCH-shift (J_{HF} Hz[d])	^{13}C NMR: FC-shift (J Hz[d])
25	2-Octyl-	15 (7)	(71)	68	9 (9)	4.62 (50)	91.1 (652)
26	2-Decyl-	15 (7)[e]	(75)	74	10 (10)	4.63 (49)	91.0 (652)
27	2-Dodecyl-	15 (7)	73[f] (74)	70	10 (14)	4.62 (50)	90.8 (652)
28	4-Decyl-	18 (10)	(65)	62	18 (12)	4.48 (49)	94.3 (662)
29	4-*tert*-Butylcyclohexyl-	15 (7[g])	(0[g])	–	14 (24)	–	–

[a] Reactions at 120°C unless otherwise specified.
[b] Based on NMR analysis of the reaction mixture using chlorobenzene as an internal standard.
[c] The overall yields of **25**, **26**, and **28** are based on undistilled fluoroformate; the overall yield of **27** is based on distilled fluoroformate.
[d] All CH resonances are doublets of multiplets; all FC resonances are doublets.
[e] Reaction at 125°C.
[f] Bp: 80°C at 2 mm.
[g] This reaction failed. Even after 24 h, no **29** was found and 55% of **15** was lost as carbonate.

The synthesis of 4-fluorodecane[23] (**28**) was examined as a model for the synthesis of less exposed secondary alkyl fluorides. As expected, the increased steric hindrance of **14** required the use of 18% HBGF and a 10 h reaction time (versus 15% HBGF for 7 h for **25**–**27**) to drive the process to completion (dry ice/CH_3CN condenser). Also, in accord with expectations, 18% of the starting **14** was lost as olefins (versus 9–10% for **25**–**27**), thus reducing the yield of **28** to 65%. The conversion of cyclohexanols to fluorocyclohexanes, a poor reaction using DAST and its analogues,[24] failed here.

To examine the mechanism of the HBGF induced conversion of alkyl fluoroformates to alkyl fluorides in greater detail, the *S*-fluoroformate (**16**) ($[\alpha]_D^{20}$ +5.1 (*c* 10.2, $CHCl_3$, ethanol free)) from *S*-(+)-2-octanol was prepared and heated for 7 h at 120°C with 15 mol% HBGF. After a workup which included removal of the alkene by-products by conversion to their high boiling

dibromides, the sample of pure 2-fluorooctane was isolated by vacuum distillation. The published $[\alpha]_D^{20}$ (*c*, 3–20, $CHCl_3$) for pure *R*-(–)-2-fluorooctane is –14.8.[25] In the present experiment, the found value for the 2-fluorooctane was –12.7 (*c* 10.0, $CHCl_3$), which translates to an optical purity of 88% (94% *R*,6% *S*) if the literature is correct.[26]

Thus, at least 88% of **25** would seem to be formed by an S_{N2} displacement with inversion of configuration at the chiral center. The remaining 12% of reaction probably occurs by an S_{N1} process (less if the departing fluoroformate releases fluoride as an ion pair). Whether the alkene side products are the result of diversion of the S_{N1} cation to an E_1 elimination or are formed by a competing E_2 elimination cannot be discerned. It is noteworthy that, while DAST gives 2-fluorooctane in 97.6% optical purity, this is overshadowed by the 50% elimination seen in that reaction.[25] The stereochemical result in the same FAR process is 88%,[25] identical to our value.

A useful new process for converting alcohols to the corresponding fluorides via fluoroformate intermediates has been described. An attractive feature is the initial fluoroformate synthesis which is essentially quantitative and affords undistilled product pure enough to use in subsequent reactions. Since fluoroformates have uses in synthesis beyond the methodology outlined here,[6,7,17] this step has value in itself. Finally, the introduction of HBGF, a highly active and potentially low cost 'naked fluoride' catalyst, is worth highlighting. A major advantage of HBGF is its substantially greater thermal stability than tetraalkylammonium fluoride catalysts, a feature which should encourage the exploration of its further applications.

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16. A solution of 18-crown 6 (3.0 mmol) in CH_3CN (20 mL) was dripped into a stirred mixture of **1** (0.027 mol) and spray-dried KF (0.20 mol) in CH_3CN (30 mL) (ice bath). The flask was topped by a dry ice/acetone condenser. As it formed, the COF_2 passed via the condenser to the bottom of a stirred 0°C collector containing 1-octanol (0.0408 mol) and dried KF (0.078 mol) in 10 mL of ether. After 2–3 h, no alcohol remained (^1H NMR) and remaining gases were flushed away with N_2. The KHF_2 and excess KF were filtered off through a silica gel plug which then was washed with 3×10 mL ether. Rotary evaporation of the filtrate (30 min at rt) afforded **3** in 100% yield (plus trace, 1.6%, ether) which was used in the next step without further purification.
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18. A reaction flask charged with HBGF (7 mol% versus **3**) attached to a small distillation apparatus topped with a septum was stirred overnight at 80°C (oil bath) under a vacuum of <1 mm of Hg. Dried N_2 was released into the system to exclude moisture and neat **3** (undistilled) was syringed in through the septum. Next, water was run through the condenser, the receiver was immersed in a dry ice/acetone bath at –50°C, and the temperature of the oil bath increased to 125°C. A little 1-fluorooctane[19] (**17**) distilled as it formed. After an hour, the oil bath temperature was increased and the remaining **17** distilled into the chilled receiver (89% yield from 1-octanol).

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