Use of C,N-chelated di-*n*-butyltin(IV) fluoride for the synthesis of acyl fluorides, fluoroformates and fluorophosgene

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ABSTRACT

$\{2-[(CH_3)_2NCH_2]C_6H_4\}(n\text{-}Bu)_2SnF$ (**1**) reacts with various chloroformates, acyl chlorides, methanesulfonyl chloride, 4,4′-dimethoxytrityl chloride and phosgene precursors or derivatives to form fluorinated analogues. All reactions proceed rapidly and under mild conditions. The use of a catalytic amount of **1** and KF in toluene led to a relatively high yield of a selected fluoroformate.

Acyl fluorides, fluoroformates and fluorinated phosgene are more stable than their chloro or bromo analogues and are useful, for example, in peptide or natural products synthesis.[1,2] Several methods have been developed for acyl fluoride synthesis. Acyl chlorides or bromides were converted to the corresponding fluorides using $(CF_3)_2Cd$,[3] Ishikawa's reagent $(CF_3CF_2CHFN(C_2H_5)_2)$,[4] aerosol fluorination,[5] SF_4 or DAST[6] and various forms of HF and other fluorides serving as fluorine sources.[7] Cyclic ketones,[8] alcohols, aldehydes,[9] carboxylic acids, acyl chlorides or *t*-Bu esters (in BrF_3)[10] can also be converted into the respective acyl fluorides.

Unfortunately, most of the reagents used for these purposes must be stored in Teflon® or copper containers, or under pressure, react very exothermically with water and also the selection of solvents which can be used with them is rather limited.

Recently, we have reported triorganotin(IV) fluorides of general formula $L^{CN}R_2SnF$, where L^{CN} is $\{2-[(CH_3)_2NCH_2]C_6H_4\}^-$ and R is alkyl (Me, *n*-Bu (**1**), *t*-Bu) or aryl (Ph) groups of different steric bulk and electronic properties.[11] These compounds are able to fluorinate titanocene dichloride essentially quantitatively. In our recent reports in this field, we described the ability of $L^{CN}(n\text{-}Bu)_2SnF$ (**1**, Fig. 1) to form di-[12] and monoorganotin(IV)[13] fluorides bearing the same or a similar ligand.[14] These compounds are presumably tri-, tetranuclear or polymeric species with rather low solubility in common organic solvents, and we used them as selective and
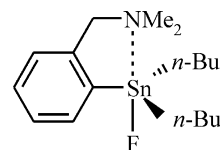

Figure 1. Structure of $L^{CN}(n\text{-}Bu)_2SnF$ (**1**).

highly sensitive carriers for fluoride ion recognition.[15] In our more recent papers, we reported the structure and fluorination ability of C,N-chelated di-*n*-butyltin(IV) fluoride (**1**, Fig. 1)[16] towards various organochlorosilanes, dichlorophenylphosphine, antimony and bismuth complexes,[17] and some metal halides.
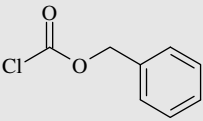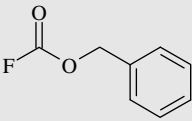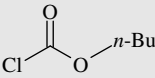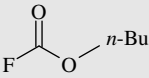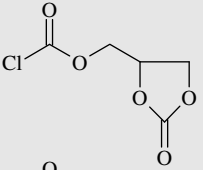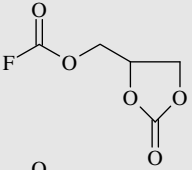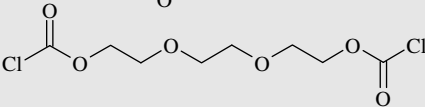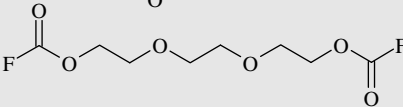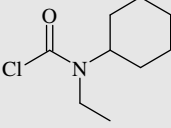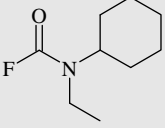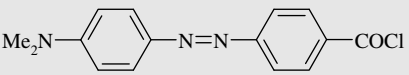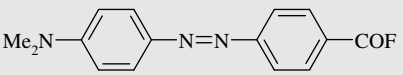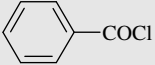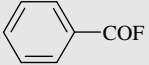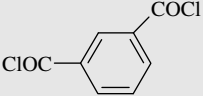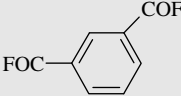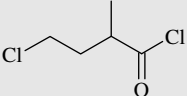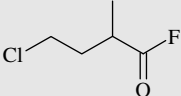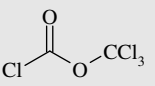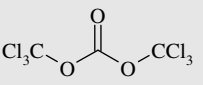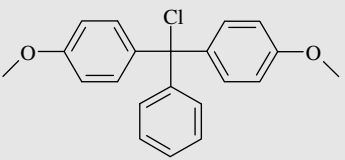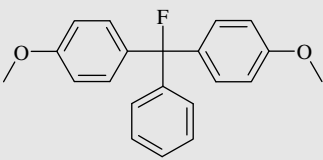
Here we communicate the high potential of C,N-chelated di-*n*-butyltin(IV) fluoride for preparing acyl fluorides, fluoroformates and other fluorides.

$\{2-[(CH_3)_2NCH_2]C_6H_4\}(n\text{-}Bu)_2SnF$ (**1**) reacts (Table 1, Fig. 2) with various chloroformates to form exclusively fluoroformates (runs 1–4), with acyl chlorides to give acyl fluorides (runs 6–13), with methanesulfonyl chloride to give its fluoride (run 14) and various phosgene precursors or derivatives to form fluorinated phosgene or thiophosgene. Di- and triphosgene gave, in the presence of moisture, fluorinated phosgene; when the reaction of triphosgene was carried out in a sealed tube, a complex composed of two $\{2-[(CH_3)_2NCH_2]C_6H_4\}(n\text{-}Bu)_2SnCl$ units and ClF_6^- was observed.[18] The reaction of 4,4′-dimethoxytrityl chloride yielded the corre-

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Table 1
Fluorination experiments

Run	Substrate	Conditions	Product	Conversion[a] (%)
1	(benzyl chloroformate)	Et$_2$O, rt, 1 equiv of **1**, 10 min	(benzyl fluoroformate)	100
2	(n-Bu chloroformate)	Et$_2$O, rt, 1 equiv of **1**, 10 min	(n-Bu fluoroformate)	100
3	(cyclic carbonate chloroformate)	Et$_2$O, rt, 1 equiv of **1**, 10 min	(cyclic carbonate fluoroformate)	100
4	(bis-chloroformate with ether chain)	Et$_2$O, rt, 2 equiv of **1**, 3 h	(bis-fluoroformate)	100
5	(N-cyclohexyl-N-ethyl carbamoyl chloride)	Toluene, reflux, 1 equiv of **1**, 12 h	(N-cyclohexyl-N-ethyl carbamoyl fluoride)	30
6	Me$_2$N—C$_6$H$_4$—N=N—C$_6$H$_4$—COCl	Benzene, rt, 1 equiv of **1**, 1 h	Me$_2$N—C$_6$H$_4$—N=N—C$_6$H$_4$—COF	100
7	(C$_6$H$_5$—COCl)	Et$_2$O, rt, 1 equiv of **1**, 1 h	(C$_6$H$_5$—COF)	100
8	(benzene-1,3-di(COCl))	Et$_2$O, rt, 2 equiv of **1**, 10 min	(benzene-1,3-di(COF))	100
9	CH$_3$COCl	Et$_2$O, 0 °C, 1 equiv of **1**, 3 h	CH$_3$COF	100
10	CH$_3$CH$_2$COCl	Et$_2$O, 0 °C, 1 equiv of **1**, 3 h	CH$_3$CH$_2$COF	100
11	ClCH$_2$CH$_2$CH$_2$COCl	Et$_2$O, rt, 1 equiv of **1**, 1 h	ClCH$_2$CH$_2$CH$_2$COF	100
12	(2-methyl-4-chlorobutanoyl chloride)	Et$_2$O, rt, 1 equiv of **1**, 1 h	(2-methyl-4-chlorobutanoyl fluoride)	100
13	CH$_3$(CH$_2$)$_7$CH=CH(CH$_2$)$_7$COCl	Et$_2$O, rt, 1 equiv of **1**, 10 min	CH$_3$(CH$_2$)$_7$CH=CH(CH$_2$)$_7$COF	100
14	CH$_3$SO$_2$Cl	Et$_2$O, rt, 1 equiv of **1**, 10 min	CH$_3$SO$_2$F	100
15	CSCl$_2$	tol.-d_8, rt, 2 equiv of **1**, 10 min	A mixture of fluorinated compounds	100
16	COCl$_2$	tol.-d_8, rt, 2 equiv of **1**, 10 min	COF$_2$	100
17	(trichloromethyl chloroformate)	tol.-d_8, rt, 4 equiv of **1**, 10 min, H$_2$O	COF$_2$	100
18	Cl$_3$C—O—CO—O—CCl$_3$	tol.-d_8, rt, 6 equiv of **1**, 10 min, H$_2$O	COF$_2$	100
19	(bis(4-methoxyphenyl)phenylmethyl chloride)	Et$_2$O, rt, 1 equiv of **1**, 30 min	(bis(4-methoxyphenyl)phenylmethyl fluoride)	100

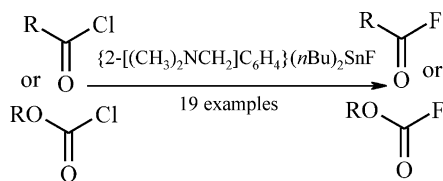[a] Directly after the reaction, based on multinuclear NMR measurements.

Figure 2. Reactivity of 1.

sponding fluorinated product almost quantitatively. All these reactions proceed rapidly under very mild conditions, and an equimolar amount of **1** is used. The process developed is selective, and chlorine atoms bonded to alkyl groups remain unchanged as demonstrated in runs 11 and 12. *N*-Cyclohexyl-*N*-ethyl carbamoyl fluoride is rather unreactive under the conditions used (run 5).

To test for a possible catalytic procedure, fluorination of tri(ethylene glycol) bis(chloroformate) was selected because of the relatively high thermal stability and boiling points of both reactant and suggested product. Ten molar equivalents of KF (530 mg), 1 M equiv of tri(ethyleneglycol) bis(chloroformate) (250 mg) and one molar percent of **1** were suspended in a reaction tube equipped with a Teflon® Young valve, in toluene. The closed tube was heated under ultrasound activation at 85 °C for one hour. The KF was filtered off and the solvent evaporated. The multinuclear NMR spectra of the yellowish oily product proved ca. 42% conversion to tri(ethyleneglycol) bis(fluoroformate). Under the same conditions but without **1**, no conversion to fluorinated product was observed.

When we tried to expand the series of compounds to different types of organic halides, we found that *tert*-butyl chloride, 1-bromooctane, benzyl bromide, 4-nitrobenzyl chloride, 2,6-dichlorobenzonitrile, 2-chlorobenzonitrile, α,α,α-trichlorotoluene, cyclohexyl and *tert*-butyl acetates did not react with **1**. Only phenyl acetate gave acetyl fluoride in 25% yield when refluxed in toluene for 20 h.

In conclusion, the advantage of reagent **1** over other systems, compounds and methods is that it has a very short reaction time and compound **1** is not volatile, is less toxic, and normal glassware can be used. Additionally, compound **1** is extremely soluble in all organic solvents, is stable in air for years, and can be recycled directly after distilling the product off by reaction with excess KF (in water/diethyl ether mixture) in very high yields (usually more than 90%).

General description of the fluorinating method: The starting substrates were dissolved in various solvents (see Table 1), and compound **1** (equimolar amount) was added in one portion. The products were separated from the reaction mixture by distillation or by trap-to-trap distillation and identified by multinuclear NMR spectroscopy and by GC/MS and ESI/MS techniques. Chromatography can also be used as a separating method, but in these cases distillation, trap-to-trap distillation and crystallization are the easiest procedures to obtain pure products. During the reaction, the composition of each reaction mixture was determined by ESI/MS techniques and the reaction was stopped when no peak for '{2-[(CH$_3$)$_2$NCH$_2$]C$_6$H$_4$}(n-Bu)$_2$SnF+H' at m/z 388 in positive ion mode was observed. The reaction progress was also monitored by ^{1}H and ^{119}Sn NMR spectroscopy.[11] The NMR spectra were recorded as solutions in C$_6$D$_6$, CDCl$_3$ or toluene-d_8 on a spectrometer (equipped with *Z*-gradient 5 mm probe) at 300 K, ^{1}H (500.13 MHz), ^{19}F{^{1}H} (470.53 MHz) and ^{119}Sn{^{1}H} (186.50 MHz).

Data for the known products are given in the Supplementary data (available online).

(2-Oxo-1,3-dioxolan-4-yl)methyl fluoroformate (**3**): ^{1}H NMR (CDCl$_3$, 295 K, ppm): 5.02–4.99 (m, 1H, CH), 4.65–4.58 (m, 2H, CH$_2$), 4.48–4.45 and 4.34–4.32 anisochronous protons (m, 2H, CH). ^{19}F{^{1}H} NMR (CDCl$_3$, 295 K, ppm): −17.7 (s). Elemental Anal. Calcd for C$_5$H$_5$O$_5$F (164.09): C, 36.6; H, 3.1. Found: C, 36.4; H, 3.0.

Tri(ethyleneglycol) bis(fluoroformate) (**4**): ^{1}H NMR (CDCl$_3$, 295 K, ppm): 4.41–4.37 (m, 4H, OCH$_2$CH$_2$O), 3.64–3.60 (m, 4H, OCH$_2$-CH$_2$O), 3.45 (s, 4H, OCH$_2$). ^{19}F{^{1}H} NMR (CDCl$_3$, 295 K, ppm): −16.8 (s). Elemental Anal. Calcd for C$_8$H$_{12}$O$_6$F$_2$ (242.18): C, 39.7; H, 5.0. Found: C, 40.0; H, 5.2.

N-Cyclohexyl-N-ethyl carbamoyl fluoride (**5**): ^{1}H NMR (CDCl$_3$, 295 K, ppm): 3.97 (t, 2H, cyclohexyl H, ^3J = 9.1 Hz), 3.86 (t, 2H, cyclohexyl H, ^3J = 9.2 Hz), 3.27 (q, 2H, ethyl CH$_2$, ^3J = 7.0 Hz), 1.76–1.68 (m, 2H, cyclohexyl H), 1.59–1.55 (m, 2H, cyclohexyl H), 1.41–0.99 (m, 6H, cyclohexyl H and ethyl CH$_3$). ^{19}F{^{1}H} NMR (CDCl$_3$, 295 K, ppm): 20.2 (s). Elemental Anal. Calcd for C$_9$H$_{16}$ONF (173.23): C, 62.4; H, 9.3; N, 8.1. Found: C, 62.7; H, 9.0; N, 8.2.

4-(4-Dimethylaminophenylazo)benzoyl fluoride (**6**): Mp 188–191 °C. ^{1}H NMR (C$_6$D$_6$, 295 K, ppm): 8.15 (d, 2H, benzoyl H, ^3J = 7.4 Hz), 7.94 (d, 2H, phenylazo H, ^3J = 5.5 Hz), 7.84 (d, 2H, benzoyl H, ^3J = 3.6 Hz), 6.39 (d, 2H, phenylazo H, ^3J = 9.0 Hz), 2.28 (s, 6H, N(CH$_3$)$_2$). ^{19}F{^{1}H} NMR (CDCl$_3$, 295 K, ppm): 21.0 (s). Elemental Anal. Calcd for C$_{15}$H$_{14}$ON$_3$F (271.30): C, 66.4; H, 5.2; N, 15.5. Found: C, 66.6; H, 5.0; N, 15.8.

4-Chlorobutyryl fluoride (**11**): ^{1}H NMR (C$_6$D$_6$, 295 K, ppm): 2.97 (t, 2H, ClCH$_2$, ^3J = 6.2 Hz), 1.95 (t, 2H, CH$_2$C(O)F, ^3J = 6.6 Hz), 1.48–1.44 (m, 2H, CH$_2$). ^{19}F{^{1}H} NMR (C$_6$D$_6$, 295 K, ppm): 45.7 (s).

4-Chloro-2-methylbutyryl fluoride (**12**): ^{1}H NMR (CDCl$_3$, 295 K, ppm): 3.40 (t, 2H, ClCH$_2$, ^3J = 6.3 Hz), 2.95–2.82 (m, 1H, CH), 2.19–2.11 and 1.90–1.80 anisochronous protons (m, 2H, CH$_2$), 1.23 (d, 3H, CH$_3$, ^3J = 7.1 Hz). ^{19}F{^{1}H} NMR (CDCl$_3$, 295 K, ppm): 38.7 (s). Elemental Anal. Calcd for C$_5$H$_8$OClF (138.57): C, 43.3; H, 5.8. Found: C, 43.1; H, 6.0.

Thiocarbonyl difluoride (**15**): Bp 54 °C (760 Torr). ^{19}F{^{1}H} NMR (tol.-d_8, 295 K, ppm): a mixture of products was observed with δ(^{19}F) at 35.7, 9.3, −27.7, −45.5, −46.7 and −50.7 ppm and five other minor signals.

Carbonyl difluoride (**16**): ^{19}F{^{1}H} NMR (tol.-d_8, 295 K, ppm): −19.3 (s).

Fluorination of diphosgene (**17**): ^{19}F{^{1}H} NMR (tol.-d_8, 295 K, ppm): −18.7 (s).

Fluorination of triphosgene (**18**): ^{19}F{^{1}H} NMR (tol.-d_8, 295 K, ppm): −19.7 (s).

4,4'-Dimethoxytrityl fluoride (**19**): ^{1}H NMR (CDCl$_3$, 295 K, ppm): 7.24 (t, 1H, phenyl H, ^3J = 6.3 Hz), 7.11 (d, 6H, phenyl H, ^3J = 8.9 Hz), 6.80–6.76 (m, 6H, phenyl H), 3.77 (s, 6H, OCH$_3$). ^{19}F{^{1}H} NMR (CDCl$_3$, 275 K, ppm): −121.3 (s).

Examples of synthesis and product separation

Benzoyl fluoride (run 1): Benzoyl chloride (0.90 g, 6.40 mmol) was dissolved in diethyl ether (30 ml) and compound **1** (2.47 g, 6.40 mmol) was added. The reaction mixture was stirred for one hour at room temperature. Afterwards, the solvent was evaporated in vacuo at 20 Torr. Pure benzoyl fluoride was distilled off (bp 159–161 °C at 760 Torr). Yield 0.72 g (91%). In the distillation residue, pure {2-[(CH$_3$)$_2$NCH$_2$]C$_6$H$_4$}(n-Bu)$_2$SnCl (2.45 g, 6.1 mmol) was identified by multinuclear NMR spectroscopy.

4-(4-Dimethylaminophenylazo)benzoylfluoride (run 6): 4-(4-Dimethylaminophenylazo)benzoyl chloride (0.50 g, 1.74 mmol) was suspended (only partially soluble) in benzene (30 ml) and compound **1** was added (0.67 g, 1.74 mmol). The reaction mixture was stirred for 1 h at room temperature, then filtered and the solid part was washed with 10 ml of hexane yielding 0.39 g (82%) of pure 4-(4-dimethyl-aminophenylazo)benzoyl fluoride. In the filtrate, after evaporation of the solvent in vacuo, essentially quantitative conversion of **1** to {2-[(CH$_3$)$_2$NCH$_2$]C$_6$H$_4$}(n-Bu)$_2$SnCl had occurred and the remainder of the 4-(4-dimethylaminophenylazo)benzoyl fluoride was observed by multinuclear NMR spectroscopy.

Acknowledgements

Supplementary data

General experimental details, data for known compounds, and ^{19}F NMR spectra of some products are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.060.

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