Novel Fluorination Reagent: IF_5 / Et_3N–3HF

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IF_5 in Et_3N–3HF was found to be a stable, non-hazardous, easy to handle, and inexpensive reagent that enables effective and selective fluorination of organic compounds under mild conditions.

A wide variety of reagents have been developed for introducing fluorine into organic compounds over the last 50 years[1] with several halogen fluorides such as ClF_3 and BrF_3 so on.[2,3] However, iodine fluorides (IF_n; n=1, 3 and 5), except for IF, have hardly been employed in organic fluorination reactions, because of their hazardousness, instability and high reactivity.[3] We describe here for the first time an efficient and convenient fluorination reagent, called IF_5 / Et_3N–3HF, (IF_5 in Et_3N–3HF solution), which is non-hazardous, easy to handle and inexpensive,[4] and selectively fluorinates organic compounds under mild conditions.

IF_5 itself is a hazardous chemical (bp 100.5 °C, mp 9.4 °C, vapor pressure: 2190 Pa at 21 °C)[5] and is very sensitive to moisture. IF_5 / Et_3N–3HF (IF_5:Et_3N:HF = 1:1:3 molar ratio),[6] on the other hand, is not sensitive to moisture and has a low vapor pressure[7] of 270 Pa at 21 °C. ^{19}F NMR spectra of IF_5, IF_5 / HF, and IF_5 / Et_3N–3HF solutions are shown in Figure 1. It is well known that IF_5 has two kinds of fluorine atoms: Fa and Fb (1:4).[8] These can be clearly assigned because of their distinct NMR shifts as shown in a and b of Figure 1. In the ^{19}F NMR spectrum of IF_5 / Et_3N–3HF, however, the two signals for Fa and Fb become extinct and a new chemical shift emerges at –53.1 ppm (broad s). On the other hand, the chemical shift is divided into two broad signals at 7.5 ppm and –160 ppm with integration ratio of 1:1 at low temperatures (–40 °C). Judging from these results, IF_5 in Et_3N–3HF solution is thought to form a novel complex. The structure of the complex has not been confirmed yet. Further investigations are necessary to clarify the structure of IF_5 / Et_3N–3HF.

Fluorination of organic compounds has been carried out according to the following procedures (A, B, C, and D). A) In a 15-mL PFA[9]-made reactor equipped with a reflux condenser and/or a cold trap, 1.2 mmol of IF_5 / Et_3N–3HF (0.46 g, ca. 0.27 mL) was added together with 4 mL of solvent. A substrates (1.0 mmol) was then added and the mixture was allowed to stand with stirring at the desired temperature and time. The reaction mixture was then quenched, neutralized with aqueous $NaHCO_3$, and washed with 10% sodium thiosulfate. The products were extracted with ether, isolated by column chromatography (silica gel / hexane–ether), and identified by conventional spectroscopic methods. B) In a 100 mL PFA-made reactor equipped with a reflux condenser and/or a cold trap, a substrate (1.0 mmol) dissolved in 20 mL of solvent was added to 1.2 mmol of IF_5 / Et_3N–3HF in 20 mL of solvent at room temperature for 1 h, and then allowed to stand with stirring at the desired temperature and time. C) The reaction mixture was prepared by adding a substrate (1.0 mmol) dissolved in a solvent (2 mL) to 1.2 mmol of IF_5 / Et_3N–3HF with 4 mL of a solvent at room temperature. D) The same procedure as C) except at –78 °C.

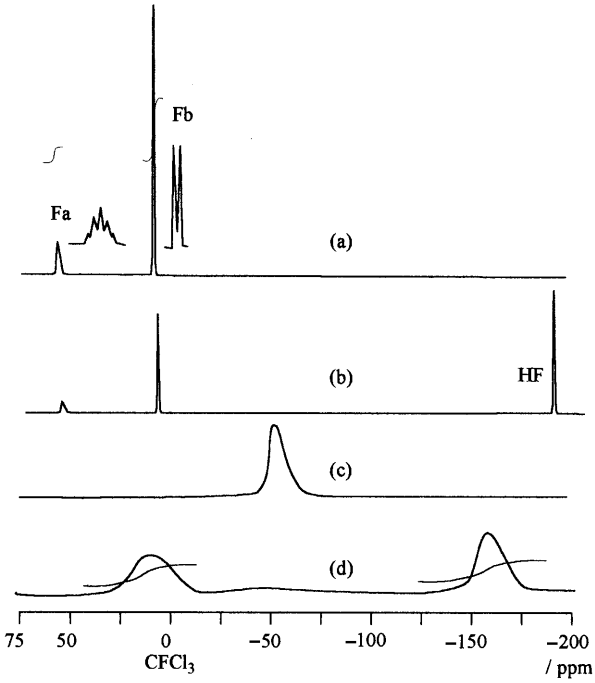
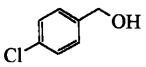
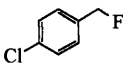
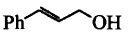
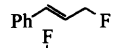
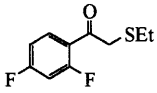
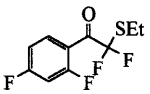
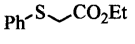
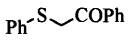
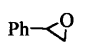
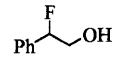
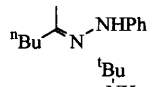
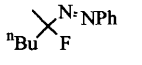
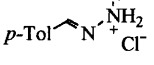
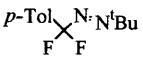
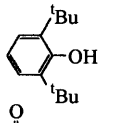
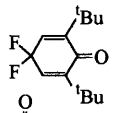
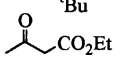
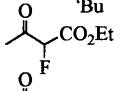
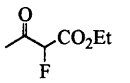
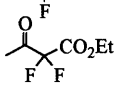


Fig.1. ^{19}F NMR spectra of IF_5 and IF_5/Et_3N–3HF.
(a) IF_5 in CH_2Cl_2 at 23 °C. (b) IF_5 / HF (molar ratio 1:6) at 23 °C. (c) IF_5/Et_3N–3HF (molar ratio 1:1) at 23 °C. (d) IF_5/Et_3N–3HF (molar ratio 1:1) at -40 °C.

The results obtained are listed in Table 1. The corresponding organo-fluorine compounds were obtained in satisfactory yields except for olefins, although the present conditions for fluorination does not give the optimum results.

Fluorinative ring-opening of epoxides and transformation of alcohols to alkyl fluorides are known to occur by reacting with amine–HF such as pyridine–9HF,[10] but, with the inevitable formation of some by-products together with tarry matter because of the high acidity of the reagents used. In addition, although tertiary and secondary alcohols are readily fluorinated in pyridine–HF, transformation of primary alcohol to the corresponding RF hardly takes place in the presence of such amine-HF reagents. It should be noted that Et_3N–3HF itself can not initiate the fluorination of all substrates listed in Table 1. In the absence of Et_3N–3HF, inevitable violent reaction of IF_5 takes place to give the considerable amount of undesirable tarry like, sometimes, carbonized mater. And selective fluorination can be accomplished by the reaction using IF_5 only in the presence of Et_3N–3HF under mild conditions. However, the mechanism

Table 1. Fluorination of Oganic Compounds Using IF_5 / Et_3N–3HF

Substrate	React. Condtions Method[a]	Temp. /°C	Time /h	Solvent	Product	Yield /%
n-C_{13}-CO_2H	A	rt	12	Heptane	*n*-C_{13}-COF	75
"	"	125	"	none	"	65
n-C_{10}-OH	"	80	48	Heptane	*n*-C_{10}-F	32
	"	rt	1	CH_2Cl_2		83
	B	"	1	Hexane		45
						22
p-Tol-SCH_3	A	100	"	Heptane	*p*-Tol-$SCHF_2$	50
	"	74	"	"		82
	A	63	4	Hexane		59
	"	"	"	"		45
	C	rt	5	CH_2Cl_2		75
PhCOPh	A	100	12	none	$PhCF_2Ph$	23
$(Ph)_2C{=}NNH_2$	B	rt	1	EtOAc	$PhCF_2Ph$	70
	D	"	0.5	"		80
	B	"	1	"		45
$PhNHNH_2$	A	"	0.5	CH_2Cl_2	PhF	30
	B	"	4	"		50
	A	40	1	"		71
	A	60	24	Hexane		25

[a] Reaction procedure: see text.

has not been clarified yet. The active species in IF_5 / Et_3N–3HF, reaction mechanism, and scope of this novel fluorination reagent are under investigation.

In conclusion, we have successfully developed an efficient, convenient and novel selective fluorination reagent, IF_5 / Et_3N–3HF, for organic compounds. We believe this novel fluorination reagent may open up a new field in the synthesis of varieties of organofluorine compounds.

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6 A prescribed amount of Et_3N–3HF was pipetted into 50–100 mmol of IF_5 in a 30-mL PFA[9] bottle without cooling since the temperature did not rise appreciably. Thus, any particular precautionary measures are not necessary for the preparation of IF_5 / 3HF–Et_3N. This reagent can be stored in PFA bottle for several months on a laboratory table without any particular caution and without any deterioration of fluorination activity.

7 Vapor pressure measurement of IF_5 / 3HF–Et_3N was carried out according to the technique described in ref 5b.

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