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A facile synthesis of organofluorine compounds using a semi-molten mixture of tetrabutylammonium bromide and an alkali metal fluoride

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Abstract

A semi-molten mixture of tetrabutylammonium bromide and an alkali metal fluoride (KF or CsF) has been found to be an efficient reagent system for the preparation of organofluorine compounds, e.g., $CH_3(CH_2)_7F$, $CH_2{=}CH{-}CH_2F$, $FCH_2CO_2C_2H_5$, C_6H_5COF, and related compounds through facile fluoride-ion exchange with organohalides. The system provides a simple and convenient alternative to 'anhydrous' tetrabutylammonium fluoride for the synthesis of oragnofluorine compounds.

Keywords: Semi-molten mixture; Tetrabutylammonium bromide; Alkali metal fluorides; Organofluorine compounds; NMR spectroscopy

1. Introduction

A number of general and convenient procedures have been developed for the synthesis of organofluorine compounds [1–3]. Amongst these, the fluoride-ion displacement of halides by metal fluorides has been most widely used, but it generally requires high temperatures and/or long reaction times. Of several methods and reagents developed recently [2,3], quaternary onium fluorides are the most attractive since they allow fluoride exchange to occur conveniently and under milder conditions; 'anhydrous' tetrabutylammonium fluoride (TBAF) has been particularly useful in several fluorination reactions [4]. However, the preparation of this reagent is rather tedious (cf. 'anhydrous' TBAF is obtained by heating commercial TBAF·$3H_2O$ at 45–50 °C, <0.1 mmHg, ca. 48 h) [4]. As an alternative, we have investigated the use of a semi-molten mixture of tetrabutylammonium bromide (TBAB) and an alkali metal fluoride (KF/CsF) as a facile fluorination reagent system, and demonstrated its application for the synthesis of organofluorine compounds in some model reactions.

2. Experimental details

Commercially available KF and CsF were finely powdered and flame-dried for 30 min while TBAB was heated under vacuum (<0.1 mmHg) at 45–50 °C for 15 min immediately prior to use. Reactions were monitored by GLC which was performed on a Shimadzu 9A gas chromatograph equipped with a 25 m×0.22 mm (i.d.) DB 1701 fused silica gel capillary column operated in a temperature mode (80–180 °C, 8 °C min^{-1}) using an FID detector and an injector port maintained at 200 °C. NMR spectra were recorded on a JEOL EX90 spectrometer in $CDCl_3$ solution using internal TMS for ^1H NMR and CF_3COOH ($\delta = -78.5$ ppm) as an external reference for ^{19}F NMR spectroscopy.

2.1. Preparation of 1-fluoro-octane: typical procedure A

Dried KF (14.5 g, 0.25 mol) and TBAB (8.05 g, 0.025 mol) were placed in a flame-dried 250 ml three-necked round-bottom flask containing a stir bar and equipped with a reflux condenser and a dry N_2 inlet. The mixture was heated at 110 °C when a semi-solid mass resulted. 1-Bromo-octane (9.65 g, 0.05 mol) was added in one portion with continued stirring. An immediate exothermic reaction was observed. The reaction was completed after stirring for 1 h. Hexane (150 ml) was added after cooling and the reaction mixture stirred for 15 min. The hexane solution was filtered and the residue extracted thrice with additional hexane (3×25 ml). The combined hexane fraction was washed with 10% HCl (75 ml) and dried (Na_2SO_4). After removal of the hexane, the product was distilled to give 1-fluoro-octane, 5.14 g (78% yield), b.p. 142 °C.

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Table 1
Synthesis of organofluorine compounds

$$R\text{–}X\ (X = Cl, Br) \xrightarrow{\text{TBAB/KF or CsF}} R\text{–}F$$

Substrate	Reaction time (min)	Method of preparation	Fluoro compounds [a]	Isolated yield (%)		Literature value yield [4] (TBAF procedure) (%)
				KF	CsF	
$C_6H_5CH_2Br$	45	A	$C_6H_5CH_2F$	86	92	66 [b]
$CH_3(CH_2)_7Br$	60	A	$CH_3(CH_2)_7F$	78	88	35 [c]
$CH_3(CH_2)_3Br$	60	B	$CH_3(CH_2)_3F$	69	77	–
C_6H_5COCl	60	A	C_6H_5COF	82	84	81
$(C_6H_5)_3CCl$	60	C	$(C_6H_5)_3CF$	91	85	65 [d]
$BrCH_2CO_2C_2H_5$	50	B	$FCH_2CO_2C_2H_5$	83	81	–
$ClCH_2CO_2CH_3$	75	B	$FCH_2CO_2CH_3$	79	73	–
CH_2=CH–CH_2Br	30	B	CH_2=CH–CH_2F	89	90	90

[a] All compounds were characterised by ^1H and ^{19}F NMR spectral data which were consistent with their structures and reported data [4,8].
[b] Side-product $C_6H_5CH_2OH$ (5% GLC); not detected in our system.
[c] Side-products $HO(CH_2)_7CH_3$ (40% GLC); CH_2=$CH(CH_2)_5CH_3$ (12% GLC); in our system 1-octanol was not formed but 1-octene (9.4% GLC) was detected.
[d] Side-product $(C_6H_5)_3COH$ (17% isolated); not detected in our system.

2.2. Preparation of ethyl 2-fluoroacetate: typical procedure B

A mixture of CsF (11.30 g, 0.074 mol) and TBAB (2.39 g, 0.0074 mol) was heated at 110 °C, and ethyl 2-bromoacetate (2.5 g, 0.015 mol) added in one portion with stirring. An exothermic reaction occurred and the mixture was stirred for a further 50 min. After completion of the reaction, the product was distilled directly to give ethyl 2-fluoroacetate, 1.28 g (81%), b.p. 119 °C.

2.3. Preparation of fluorotriphenylmethane: typical procedure C

A mixture of KF (9.3 g, 0.16 mol) and TBAB (5.16 g, 0.016 mol) was heated at 110 °C, and chlorotriphenylmethane (9 g, 0.032 mol) added in one portion with stirring. The mixture was stirred for a further 1 h, cooled and extracted with diethyl ether. The solid obtained on removal of ether was washed with ice water and filtered under suction. The product was crystallised from hot hexane to give fluorotriphenyl methane, 7.7 g (91%), m.p. 103 °C.

3. Results and discussion

A mixture of TBAB (m.p. 103–104 °C) and alkali metal fluoride (KF or CsF) in a 0.5:5 mole ratio forms a semi-molten mass on heating at 110 °C. The addition of organohalide (1 mol) to the molten mass leads to an exothermic reaction. Fluoride exchange is facile and the products may be isolated either by direct distillation from the reaction mixture (procedure B), solvent extraction followed by distillation (procedure A) or crystallisation (procedure C). The compounds synthesised are listed in Table 1, and their physical and ^{19}F spectral data are given in Table 2. The ^1H and ^{19}F NMR spectral data were consistent with the assigned structures and the reported literature values.

Organofluorine compounds are produced in high yield with alkyl, aralkyl and alkenyl halides in our method; both KF and CsF in combination with TBAB were equally effective in fluorination reactions. From the GLC analysis of the reaction mixtures, it was observed that a small amount of tributylamine (6%–8%) was generated during the reaction. However, no other significant side-products, e.g. alcohols, were observed. Thus 1-octanol, triphenylmethanol or benzyl alcohol were not detected in our reactions, while these were significant side-products in similar reactions with anhydrous TBAF [4]. Nevertheless, a small amount of 1-alkene was formed (by elimination catalysed by the fluoride ion) along with 1-fluoroalkane in reactions with alkyl halides, e.g. 1-octene was generated in the reaction of 1-bromo-octane with TBAB/KF mixture (GLC analysis: 1-fluoro-octane, 84%; 1-octene, 9.4%; tributylamine, 6.6%).

Fluorination reactions presumably occur through in situ generation of TBAF from the exchange of TBAB with alkali metal fluoride in the system described. In this molten mass, the fluoride ion is likely to be unsolvated and hence more reactive [5] than even anhydrous TBAF which contains 0.1–0.3 mol equiv. of water [4]. However, the formation of HF_2^- through decomposition of in-situ generated TBAF [6,7] and its subsequent participation in the fluorination reaction cannot be ruled out. This is also indicated by the fact that small amounts of tributylamine were also generated in our reactions during the formation of organofluorine compounds.

4. Conclusion

In conclusion, the semi-molten mixture of TBAB and KF or CsF is a facile reagent system for the fluoride-ion displacement reaction on organohalides. The method is simple and

Table 2
Physical and ^{19}F NMR spectral data for compounds synthesised

Compound	B.p./[m.p.] (°C)		δ_F (ppm)		$^2J_{H-F}$ (Hz)	
	Observed	(Lit. value)	Observed	Lit. value [4,8]	Observed	Lit. value [4,8]
$C_6H_5CH_2F$	141	(140) [9]	−206.8	−206.4	47.8	48.5
$CH_3(CH_2)_7F$	142	(142–143) [10]	−218.5	−218.5	48.8 (^3J=24.4 Hz)	47.5 (^3J=23.3 Hz)
$CH_3(CH_2)_3F$	32–33	(32.5) [11]	−218.5	−218.6	47.8 (^3J=25.3 Hz)	48.2 (^3J=25.0 Hz)
C_6H_5COF	160–161	(159–161) [12]	+17.7	+18.2	–	–
$(C_6H_5)_3CF$	[103]	(102–104) [4]	−126.7	−126.2	–	–
$FCH_2CO_2C_2H_5$	119	(117–121) [13]	−230.5	−228.0	48.8	47.0
$FCH_2CO_2CH_3$	104–105	(104.5) [13]	−230.7	–	48.8	–
CH_2=CH–CH_2F	–[a]	(−3) [14]	−216.2	−216.7	47.0 (^3J=15.2 Hz)	46.3 –

[a] Not recorded, product collected in a cooled weighed flask by entrainment in a stream of dry nitrogen [4] characterised by spectral data.

convenient and can be considered as an alternative to 'anhydrous' TBAF in the synthesis of organofluorine compounds providing several advantages such as higher yield of the fluorinated products obtained, no prior reagent preparation, short reaction times and the absence of side-reaction products commonly encountered with other reagents. The further scope of this system is presently under investigation.

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