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A semi-molten mixture of hexadecyltributylphosphonium bromide and potassium fluoride in the synthesis of organofluorine compounds

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Abstract

A facile and effective reagent system comprising of a semi-molten mixture of hexadecyltributylphosphonium bromide and potassium fluoride has been developed and its scope has been investigated in nucleophilic fluoride exchange with various organohalides. This simple and convenient reagent system provides organofluorine compounds in high yields even with haloesters in which fluoride catalysed elimination is also feasible. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Semi-molten mixture; Hexadecyltributylphosphonium bromide; Organofluorine compounds

1. Introduction

Amongst several methods and reagents developed recently for the synthesis of organofluorine compounds, quaternary onium fluorides are the most attractive since they allow fluoride exchange to occur conveniently and under milder conditions [1,2]. Such reagents include tetrabutylammonium fluoride (TBAF), tetramethylammonium fluoride (TMAF), benzyltrimethylammonium fluoride (BTMAF) and tetrabutylphosphonium fluoride (TBPF), of which TBAF has received most attention for fluorination reactions [3]. However, the preparation of 'anhydrous' TBAF is rather tedious and as an alternative, we earlier investigated the use of a semi-molten mixture of tetrabutylammonium bromide (TBAB, m.p. 103-104°C) 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 [4]. During our further investigations on the scope of this reagent it was observed in some halo esters that along with the nucleophilic fluoride exchange, the elimination reaction catalysed by F⁻ as a base was significant, resulting in overall lowering of the yield of organofluorine compounds. Therefore, we have investigated the semi-molten mixture of another significantly low melting onium salt hexadecyltributylphosphonium bromide (HTPB, m.p. 56-58°C) and

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potassium fluoride in the synthesis of organofluorine compounds, including examples in which elimination reactions are feasible and compared the results with TBAB/KF system. The findings have been discussed in this paper.

2. Experimental details

Commercially available KF was finely powdered and flame-dried for 30 min; HTPB was dried under vacuum (<0.1 mm Hg) at 40–45°C for 15 min immediately prior to the reaction. The details of monitoring of the reactions by GLC and characterisation of compounds by ¹H and ¹⁹F NMR have been described earlier [4]. The mass spectra were recorded on a Finnigan Mat, TSQ 7000 mass spectrometer.

2.1. Preparation of 4-bromobenzyl fluoride: typical procedure A

Dried KF (15 g, 0.26 mol), HTPB (13.1 g, 0.026 mol) were placed in a flame-dried 250 ml round bottom flask containing a stir bar and equipped with a reflux condenser and a dry N₂ inlet. The mixture was heated at 60°C when a semi solid mass resulted. 4-Bromobenzyl bromide (12.9 g, 0.052 mol) was added in one portion with continued stirring. The reaction was completed after stirring for 30 min. Hexane (150 ml) was added after cooling and the reaction mixture stirred for 10 min. The hexane solution was filtered and the residue extracted thrice with additional hexane (3 × 25 ml). After removal of hexane, the crude product

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obtained was purified by recrystallisation from the same solvent to give 4-bromobenzyl fluoride, 6.6 g (68% yield), m.p. $14-16^{\circ}C$.

2.2. Preparation of methyl 2-fluoropropionate: typical procedure B

A mixture of KF (10.0 g, 0.17 mol), HTPB (8.7 g, 0.017 mol) was heated at 60° C and methyl 2-bromopropionate (5.7 g, 0.034 mol) was added in one portion with stirring. An exothermic reaction occurred and mixture was stirred for a further 45 min. After completion of the reaction, the product was distilled directly to give methyl 2-fluoropropionate, 2.9 g (80%), b.p. 110°C.

3. Results and discussion

The low-melting onium salt HTPB and potassium fluoride were taken in a 0.5:5 mol ratio; the mixture on heating at 60° C formed a semisolid mass. The addition of organohalide (1 mol) to the molten mass led to an exothermic reaction. Fluoride exchange was facile and the products were isolated from reaction mixture either by direct distillation from the reaction mixture (procedure B) or by

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Synthesis of organofluorine compounds

solvent extraction followed by distillation (procedure A). The compounds synthesised are listed in Table 1, among these 2-fluoroethanol, methyl 2-fluoropropionate and ethyl 2-fluoropropionate were isolated by procedure B and others were worked up by procedure A. The physical and spectral data are given in Table 2. The ¹H, ¹⁹F and mass spectral data were consistent with their assigned structure.

The semi-molten mixture of HTPB/KF produces organofluorine compounds from alkyl, aralkyl halides and haloesters. The reaction was found to be facile and completed in 30–60 min as observed by the GC analysis of the reaction mixture. The isolated yields of the compounds shown in Table 1 are unoptimised. The aryl halide, however, did not react in the case of bromobenzene. Cyclohexyl bromide on the other hand gave only an elimination product, cyclohexene and no fluoro compound could be detected.

A comparative study of the HTPB/KF reagent with our previously described TBAB/KF system was carried out; the reactions were run for the same period of time. The alkyl and aralkyl halides such as 2-bromoethanol, 4-bromobenzyl bromide and diphenyl bromomethane involving predominantly nucleophilic fluoride exchange reaction, gave good yield of the corresponding fluoro compounds. Even though yields were slightly better with the HTPB/KF reagent, in view of the fact that yields were unoptimised, the two

Substrate	Reaction time (min)	Fluoro compounds ^a	Isolated yield (%) ^b	Isolated yield (%) ^b		
			present method	TBAB method [4]		
Br-CH2-CH2OH	30	F-CH ₂ -CH ₂ OH	70	61		
$Br-CH(C_6H_5)_2$	45	$F-CH(C_6H_5)_2$	67	52		
$Br-CH_2C_6H_4-Br(p)$	30	$F-CH_2C_6H_4-Br$ (p)	68	57		
CH ₃ CHBrCO ₂ CH ₃	45	CH ₃ CHFCO ₂ CH ₃	80	16		
CH ₃ CHBrCO ₂ C ₂ H ₅	45	CH ₃ CHFCO ₂ C ₂ H ₅	80	4		
CH ₃ CH ₂ CHBrCO ₂ C ₂ H ₅	45	CH ₃ CH ₂ CHFCO ₂ C ₂ H ₅	89	2		
CH ₃ CH ₂ CH ₂ CHBrCO ₂ C ₂ H ₅	45	CH ₃ CH ₂ CH ₂ CHFCO ₂ C ₂ H ₅	78	5		
BrCH ₂ CH ₂ CH ₂ CO ₂ C ₂ H ₅	45	FCH ₂ CH ₂ CH ₂ CO ₂ C ₂ H ₅	60	c		
cyclo-C ₆ H ₁₁ Br	30	no fluorocompound ^d	0	0		
Br-C ₆ H ₅	60	no fluorocompound ^e	0	0		

^a All compounds were characterised by ¹H and ¹⁹F NMR, and mass spectral data which were consistent with their structure and reported data [5–9]. ^b Yields are unoptimised.

^c Reaction not studied.

^d Cyclohexyl fluoride was not formed, instead cyclohexene (100%, GC yield) was formed.

^e Fluorobenzene not formed, no fluoride exchange observed.

Table 2

Physical characteristics,	19F NMR	and mass	spectral	data for	compounds	synthesised

Compounds	b.p./[m.p.] (°C)	$\delta_{\rm F}$ (ppm)	$^{2}J_{\mathrm{H-F}}$ (Hz)	MS (El, 70 eV) <i>m</i> / <i>z</i> (Rel. Int. %)
FCH ₂ -CH ₂ OH	104	-226.52	47.8	64 (M ⁺ , 53.0); 33(9.53); 31(100.0)
$FCH-(C_6H_5)_2$	88–90/0.3 mm Hg	-165.77	48.8	186 (M ⁺ , 2.0); 185(10.3); 167(8.1); 105(100.0); 77(69.0)
$FCH_2-C_6H_4-Br$ (p)	[14–16]	-207.62	47.8	188/190 (M ⁺ , 100/98); 109 (67.3); 33(29.1)
CH ₃ CHFCO ₂ CH ₃	110	-184.89	46.4	106 (M ⁺ , 7.5); 75(15.1); 47(100.0)
CH ₃ CHFCO ₂ C ₂ H ₅	121	-184.56	47.8	120 (M ⁺ , 6.1); 75(77.3); 47(52.5); 29(100.0)
FCH ₂ CH ₂ CH ₂ CO ₂ C ₂ H ₅	151	-219.89	48.8	134 (M ⁺ , 4.1); 89(100.0); 61(19.3)
CH ₃ CH ₂ CHFCO ₂ C ₂ H ₅	138	-193.67	48.8	134 (M ⁺ , 8.3); 128(31.3); 55(100.0)
CH ₃ CH ₂ CH ₂ CHFCO ₂ C ₂ H ₅	152	-192.13	48.9	148 (M ⁺ , 1.5); 128(31.3); 55(100.0)

procedures can be considered to be equally effective. The new reagent HTPB/KF, however, offers distinct advantage in cases of haloesters where organofluorine compounds were obtained in much higher yields in comparison to TBAB/KF reagent (Table 1) in spite of the fact that in these cases besides halogen exchange, a fluoride catalysed elimination reaction can also occur leading to an overall reduced yield of the organofluorine compound. This may presumably be due to a lower reaction temperature with HTPB (60°C) compared to TBAB (110°C) thereby resulting in lesser elimination reaction catalysed by fluoride as a base. This is illustrated by the GC analysis of the reaction mixture of a α -haloester reacted separately with the two reagents for the same time period. Thus, methyl 2-bromopropionate produced 99% (isolated yield 80%) of the corresponding fluoro compound accompanied by only 1% of methyl acrylate resulting from the F⁻ catalysed elimination when reaction was carried out with HTPB/KF. On the other hand, GC analysis of the reaction mixture carried out with TBAB/ KF showed 26% methyl 2-fluoropropionate (isolated yield 16%), 36% methyl acrylate, 38% other products including tributylamine and unreacted starting material. Similar advantage has also been observed in case of reaction with ethyl 4-bromobutyrate, an example of a γ -haloester.

4. Conclusion

In conclusion, the semi-molten mixture of HTPB and KF is a facile reagent for the fluoride exchange reaction

with organohalide. The method is simple and convenient. The method is similar to TBAB/KF in cases where nucleophilic fluoride exchange is a predominant reaction. However, the present method has an advantage in the case of haloesters wherein the fluoro compounds are obtained in considerably higher yields as fluoride catalysed elimination products are reduced possibly due to the lower reaction temperature.

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