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Acceleration of the Fluorination of Benzyl Halide by the Combination of Lead Fluoride and Sodium Salt

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A new composite reagent, a combination of lead fluoride (PbF_2) and a small amount of sodium salt (NaX, X=F, Br etc.) was found to be useful for facilitating heterogeneous fluorination of substituted benzyl halides in acetonitrile.

The use of inorganic solid surface in organic reactions is a rapidly growing area of interests owing to its possibility of the control of reactivity and/or selectivity.[1] We have recently studied novel solid-liquid interfacial fluorination methodology by means of composite inorganic solid materials. For instance, the potassium fluoride-calcium fluoride combined reagent is much more efficient for the fluoride displacement of organic halides than potassium fluoride alone.[2] In addition, the combination of aluminum fluoride with alkali metal hydrogen fluoride or ammonium hydrogen fluoride enhances the ring opening of epoxides to fluorohydrins or the addition of halogenofluoride to a carbon-carbon double bond.[3] In this paper, we report that the combined use of lead(II) fluoride with a small amount of sodium salt accelerates the solid-liquid interfacial substitution reaction of substituted benzyl halides to the corresponding fluorides in acetonitrile.

Lead(II) fluoride, PbF_2, which has low reactivity in comparison with lead(IV) fluoride, has scarcely been used as fluorinating reagents in organic reactions so far.[4] The heterogeneous substitution of benzyl bromide using 2.5 molar equiv of commercial PbF_2 powder proceeded sluggishly in acetonitrile at 90 °C for 72 h to give only a 23 % yield of benzyl fluoride (Table 1, entry 1). In contrast, the combined use of PbF_2 with 10 mol% of sodium fluoride (NaF) afforded the fluorinated product in 79 % yield under the same reaction conditions (entry 3).[5,6] Figure 1 obviously shows the acceleration by this combined use. However, the addition of other alkali metal fluoride, LiF or KF, to PbF_2 did not induce such acceleration (entries 2,4).

Table 1. Effect of Alkali Metal Fluorides on the Fluorination of Benzyl Bromide by PbF_2[a)]

Entry	Additive	GLC yield of $PhCH_2F$ / % (Time / h)			
1	none	11 (24)	17 (48)	23 (72)	28 (96)
2	LiF	9 (24)	15 (48)	19 (72)	
3	NaF	36 (24)	72 (48)	79 (72)	
4	KF	20 (24)	23 (48)		39 (96)

a) $PhCH_2Br$ (1 mmol), PbF_2 (2.5 mmol), Additive (0.25 mmol) in CH_3CN at 90 °C.

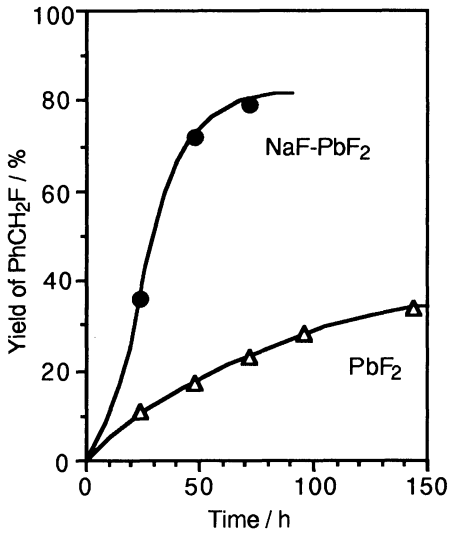


Fig. 1. The fluorination of benzyl bromide by the NaF-PbF_2 reagent.

Effect of various sodium salts other than NaF has been also investigated on the above fluorination. As shown in Table 2, the reactivity of the combined solid reagents varied either in a positive or negative direction depending on sodium salts. The presence of sodium salt of F^-, Br^-, Cl^-, HF_2^-, or CO_3^{2-} was found to be effective for the acceleration of the fluorination of benzyl bromide by PbF_2.

On increasing the NaBr/PbF_2 molar ratio from 0.1 to 0.4, the reactivity of the NaBr-PbF_2 reagent was remarkably depressed to give only a 5 % yield of the product after 72 h. Even in this case, however, the fluorination did proceed smoothly when the solid mixture of NaBr and PbF_2 was stirred in acetonitrile at 90 °C for 24 h before the addition of the substrate; the product was formed in 61 % yield after 72 h. On decreasing the

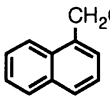
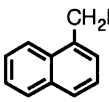
Table 2. Effect of Sodium Salts on the Fluorination of Benzyl Bromide by PbF_2[a)]

Entry	Additive	Glc yield of $PhCH_2F$/% (Time/h)		
1	NaBr	25 (24)	61 (48)	80 (72)
2	NaCl	11 (24)	46 (48)	62 (72)
3	$NaHF_2$	22 (24)	63 (48)	77 (72)
4	Na_2CO_3[b)]	24 (24)	50 (48)	65 (72)
5	NaI	2 (24)	7 (48)	
6	$NaClO_4$	1 (24)	6 (48)	
7	Na_2SO_4[b)]	2 (24)	3 (48)	6 (72)

a) $PhCH_2Br$ (1 mmol), PbF_2 (2.5 mmol), Additive (0.25 mmol) in CH_3CN at 90 °C. b) Additives (0.125 mmol).

$NaBr/PbF_2$ molar ratio from 0.1 to 0.04, on the other hand, the reactivity of the composite reagent remained unchanged. The reactivity further increased when this reagent was treated in CH_3CN at 90 °C for 24 h before the reaction.[7] This composite reagent ($NaBr/PbF_2$=0.04 molar ratio) was found to facilitate the fluorination of several substituted benzyl and allilic halides as shown in Table 3.

Table 3. Solid-Liquid Interfacial Fluorination Using the $NaBr\text{-}PbF_2$ Reagent[a]

Substrate	Time	Product	Yield / %[b]
$C_6H_5CH_2Br$	48 h	$C_6H_5CH_2F$	75 (56)
p-$MeC_6H_4CH_2Br$	24 h	*p*-$MeC_6H_4CH_2F$	83
p-$BrC_6H_4CH_2Br$	48 h	*p*-$BrC_6H_4CH_2F$	64
m-$ClC_6H_4CH_2Br$	120 h	*m*-$ClC_6H_4CH_2F$	71 (64)
p-$NO_2C_6H_4CH_2Br$	120 h	*p*-$NO_2C_6H_4CH_2F$	73 (66)
p-$MeC_6H_4CH_2Cl$	96 h	*p*-$MeC_6H_4CH_2F$	56
	32 h		56
$C_6H_5CH=CHCH_2Br$	5 h	$C_6H_5CH=CHCH_2F$	41

a) Substrate (1 mmol), $NaBr/PbF_2$ (0.1 / 2.5 mmol) in CH_3CN at 90 °C. The $NaBr\text{-}PbF_2$ reagent was previously treated by stirring in CH_3CN at 90 °C for 24 h.

b) Isolated yields are shown in parentheses, and the others are those determind by ^{19}F NMR using an internal standard.

In the case of crotyl bromide, the S_N2 and S_N2' products were formed in the ratio 1 : 2 by the use of our reagent, whereas no rearrangement was observed by the use of KF-18-crown-6. The detailed results will be published elsewhere. The solid reagent was not effective for the fluorination of simple alkyl bromides under similar reaction conditions.

The powder X-ray diffraction analysis indicated that the pretreatment of the $NaBr\text{-}PbF_2$ reagent with heating at 90 °C in CH_3CN resulted in the formation of a trace amount of new inorganic compound. This result suggests that some chemical interaction between the two solids, PbF_2 and NaBr, takes place, which may explain the observed effect. Further elucidation of the acceleration mechanism is currently under way.

In conclusion, our composite reagent, whose reactivity is not so high at present but enough to introduce fluorine to benzylic position, is novel and promising in a sense that a small amount of additives greatly influences on less reactive lead fluoride to enhance the solid -liquid interfacial reaction.

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5) The two samples of PbF_2 has been used in the experiments, one from Aldrich, the other from Morita Kagaku. Both samples gave very similar results. We thank Morita kagaku Kogyo Co., Ltd. for the contribution of PbF_2.

6) A small amount of N-benzylacetamide was formed as a by-product from benzyl bromide and acetonitrile.

7) Pretreatment of the solid mixtures by ultrasonic irradiation in acetonitrile at 60 °C was not effective for this composite reagent.

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