AN IMPROVED AND PRACTICAL SYNTHESIS OF 4-FLUOROBENZALDEHYDE BY HALOGEN-EXCHANGE FLUORINATION REACTION

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SUMMARY

A process which can afford a large quantity of 4-fluorobenzaldehyde was developed from halogen-exchange of 4-chlorobenzaldehyde with potassium fluoride in aromatic hydrocarbon solvents in the presence of tetraphenylphosphonium bromide plus polyethylene glycol dimethyl ether. The features of the reaction are discussed.
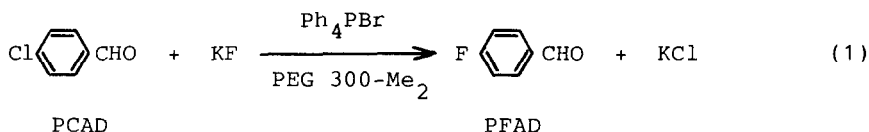
INTRODUCTION

In this paper, we show that halogen-exchange fluorination proceeds smoothly in aromatic hydrocarbon solvents in the presence of tetraphenylphosphonium bromide plus polyethylene glycol dimethyl ether.

4-Fluorobenzaldehyde (PFAD) is an attractive aromatic fluoride compound as a synthetic intermediate, because its formyl group can be easily converted to other functional groups. However, probably due to difficulties which would be encountered for obtaining 4-fluorobenzaldehyde on a large scale, it has been little exploited so far.

The reported methods for the synthesis of fluorobenzaldehyde congeners consist of 1) an oxidation reaction [1] of the methyl group of fluorotoluene derivatives synthesized by the Balz-Schiemann reaction [2] and related reactions [3], 2) oxidation of fluorobenzyl alcohols [4] or fluorophenylacetic acid [5], and 3) reduction of fluorobenzonitriles [6], these

reactions seem to be inapplicable to the large scale prepara-
tion of fluorobenzaldehyde derivatives due to use of unstable
intermediates [2], toxic anhydrous hydrogen fluoride [2-5],
and many synthetic steps [6].

$$Cl\langle\bigcirc\rangle CHO \quad + \quad KF \quad \xrightarrow[\text{PEG 300-Me}_2]{\text{Ph}_4\text{PBr}} \quad F\langle\bigcirc\rangle CHO \quad + \quad KCl \qquad (1)$$

   PCAD   PFAD

We have recently developed a convenient synthetic route to
4-fluorobenzaldehyde from 4-chlorobenzaldehyde (PCAD) by
halogen-exchange in the absence of solvent, in which the reac-
tion catalyzed by a combination of tetraphenylphosphonium
bromide (Ph_4PBr) plus 18-crown-6 or polyethylene glycol
dimethyl ether [7] (eq. 1). While the method seems to be
attractive in synthetic chemistry because of the ready availa-
bility of the starting materials and its experimental
simplicity, use of appropriate solvents is much better on an
industrial scale. However, the fluorination reaction could
not be applied in dipolar aprotic solvents such as sulfolane
and N-methylpyrrolidone which are usually used on a halogen-
exchange fluorination reactions and instead give a large
amount of tarry materials (vide infra).
 Therefore, our attention was next focused on the investi-
gation of appropriate solvents for PFAD synthesis by halogen-
exchange.
 We now report the results of a comprehensive study of
solvent effects on these reactions.

RESULTS AND DISCUSSION

 Treatment of PCAD with spray dried potassium fluoride in
sulfolane at 200 $^{\circ}$C for 12 h gave PFAD in less than 5% yield.
The yield of the desired product did not increase with
prolonged reaction time. Application of the Ph_4PBr/KF reagent
system recently developed by Prof. Clark [8] was next attempt-
ed. Thus, a mixture of PCAD with 1.5 equiv. of spray dried KF
was stirred at 210 $^{\circ}$C in the presence of 0.1 equiv. of Ph_4PBr
in sulfolane or N-methylpyrrolidone. Although the reaction in

sulfolane in the presence of Ph_4PBr gave PFAD in 49% yield, large amounts of tarry materials were also produced (Table 1, run 11). The reaction mixture gradually became a highly viscous liquid. Reaction in N-methylpyrrolidone did not give the desired product even in the presence of Ph_4PBr (Table 1, run 8). In these cases the effect of 18-crown-6 or poly-ethylene glycol dimethyl ether was not investigated.

We have now found that use of some aromatic solvents as less polar solvents was applicable to give PFAD in good yield. Treatment of PCAD with 1.5 equiv. of spray dried KF in the presence of catalytic amounts of Ph_4PBr in 1-chloronaphthalene as solvent gave PFAD in 54% yield with 43% of unreacted starting materials (Table 1, run 1). The reaction was very clean without tarry materials. In the absence of Ph_4PBr, no detectable reaction was observed. In this solvent system, combination of Ph_4PBr and polyethylene glycol dimethyl ether having an average molecular weight 300 ($PEG\ 300\text{-}Me_2$) showed significantly greater activity than Ph_4PBr alone (Table 1, runs 1-3). Some other solvents were tested for PFAD synthesis as summarized in Table 1. Aromatic solvents except for tetra-hydronaphthalene were generally useful. Reaction times depended strongly upon the nature of potassium fluoride (Table 1, runs 5 and 6).

A further advantage of the use of aromatic hydrocarbon solvents is that expensive tetraphenylphosphonium halide (Ph_4PX) could be easily recovered from the residue after distillation of product and unreacted PCAD. By ion chromato-graphic analysis, it was found that the recovered phosphonium salt from the reaction performed in 1-chloronaphthalene is a mixture of Ph_4PBr and Ph_4PCl (ca. 1:1). Ph_4PF was not present.

Reuse of expensive Ph_4PX was next examined. Two methods were attempted. The first was direct reuse of recovered catalyst. A mixture of the recovered phosphonium salt and a small amount of virgin Ph_4PBr was used as catalyst under the same reaction conditions as previously and the yield of the desired PFAD fell off slightly (Table 2, run 2). The second method was recycling of the residue including Ph_4PX and $PEG\ 300\text{-}Me_2$. Thus, to the distillation residue of run 2 were

TABLE 1

Preparation of 4-fluorobenzaldehyde (PFAD) catalyzed by tetraphenylphosphonium bromide[a]

Run	Solvent	KF[b] (1.5 equiv.)	Additive (0.05 equiv.)	Time h	Yield/%[c] PFAD	Yield/%[c] unreacted PCAD
1	1-chloronaphthalene	M	none	5	54	43
2	"	M	$CH_3O(CH_2CH_2O)_4CH_3$[d]	7	73(68)	15(11)
3	"	M	PEG 300-Me$_2$	5	64(60)	31
4	methylnaphthalene (mixture of 1- and 2-)	M[e]	"	7	—(61)	—
5	3,4-dichlorotoluene	M	"	5	75	f
6	"	L	"	14	56	f
7	triethylene glycol dimethyl ether	L	"	5	25	58
8	N-methylpyrrolidone	L	"	8	7	54
9	nonanonitrile	L	"	5	10	63
10	tetrahydronaphthalene	L	"	5	trace	f
11	sulfolane	L	"	3	49	5

[a] The reactions were conducted by stirring a mixture consisting of 100 mmol of PCAD, 150 mmol of KF, 10 mmol of Ph$_4$PBr, and additive in 20 ml of solvent at 210 °C.   [b] M=Spray dried KF purchased from Morita Kagaku Kogyo Co.; L=spray dried KF purchased from Laporte Industry Co..   [c] Yields were determined by GLC using internal standard techniques, and those in parentheses are for isolated products.   [d] 0.2 equiv. of tetraethylene glycol dimethyl ether was used.   [e] 1.78 equiv. of KF was used.   [f] Could not be determined by GLC because of overlap with the solvent.

added PCAD, KF, and the same amount of virgin Ph_4PBr as in run 2. The reaction mixture was heated with stirring under the same conditions as run 1 to afford 73% yield of PFAD (Table 2, run 3). The recycling process of the residue seems to give good yield according to these preliminary experiments.

As benzaldehyde derivatives are generally reactive species for instance undergoing the Cannizzaro reaction under basic conditions, direct halogen-exchange reactions of chlorobenzaldehyde derivatives by alkali metal fluorides which are strong bases in organic synthesis have not been explored [9]. It is surprising that the reaction of benzaldehyde derivatives and KF can proceed smoothly in aromatic solvents. The preparation of fluorobenzaldehyde derivatives from the corresponding chlorides by KF containing small amounts of cesium fluoride in dipolar aprotic solvents was recently reported in a Patent [10]. We tried the reaction of PCAD with spray dried KF containing 0.05 equiv. of cesium fluoride in sulfolane at 215 °C overnight according to the literature. The results afforded PFAD in only 4% yield and the reaction mixture became a highly viscous liquid in our hands.

The precise reaction mechanism of the novel catalytic fluorination is at present unclear. We do not believe this fluorination reaction proceeds by the usual phase-transfer mechanism for the following reasons. (1) Ph_4PF was not found in the recovered phosphonium salt. (2) The recovered phosphonium salt was 1:1 mixture of chloride and bromide. If Ph_4PF is a real intermediate, the recovered phosphonium salt should be the chloride. (3) Ph_4PF is not a useful fluorination agent owing to its lower solubility and very hygroscopic substance [11]. We now believe that the catalytic reaction proceeds through a Meisenheimer intermediate which is stabilized by Ph_4PBr [12].

As mentioned above, we have observed that addition of polyethylene glycol dimethyl ether enhances the reactivity of the potassium fluoride. The role of the polyether may be to enhance a formation of naked fluoride [13].

The new method includes the following advantages over the original procedures. (1) The use of aromatic solvents is more

practical in an industrial preparation as it allows effective stirring. The original procedure without solvent is clearly not applicable to large scale synthesis. (2) Problems associated with the use of dipolar aprotic solvents are that such solvents are expensive, toxic, easily decompose at high temperature in the presence of fluoride ion, and present difficulties in product separation and purification. (3) The expensive tetraphenylphosphonium salt (Ph_4PX) can be recovered in high yield. The phosphonium salt was decomposed and could not be recovered after reaction in sulfolane or without solvent. (4) Selectivity of the desired product was improved because of decreased formation of tarry materials.

By employing these improved synthetic methods, we have succeeded in readily obtaining a large quantity of PFAD from PCAD.

TABLE 2

Recovery of catalyst[a]

Run	Ph_4PX	$CH_3O(CH_2CH_2O)_4CH_3$	Yield/%	
			PFAD	PCAD
1	4.2 g of Ph_4PBr	yes	73	15
2	3.0 g of recovered salt plus 1.2 g of virgin Ph_4PBr	yes	66	21
3	after distillation of run 2 plus 1.2 g of virgin Ph_4PBr	no	73	18

[a] The reaction was conducted by stirring a mixture consisting of 100 mmol of PCAD, 150 mmol of KF, 10 mmol of Ph_4PBr, 20 mmol of tetraethylene glycol dimethyl ether, and 20 ml of 1-chloronaphthalene at 210 °C for 7 h. Yields were determined by GLC.

EXPERIMENTAL

Product mixtures were analyzed by GLC on a Hitachi Model 163 gas chromatograph using a 3 mm x 2 m column of Dexsil 400 GC on Chromosorb W AW DMCS (used of cyclododecane as an

internal standard). Recovered tetraphenylphosphonium salts were analyzed on a Yokokawa Hokushin Electric Ion Chromatographic Analyzer. The temperature of the oil bath used was controlled with the aid of Ricoh Mini Heater Electric Controller Model MH-10.

Unless stated otherwise, all reagents and chemicals were obtained commercially and used without further purification. 4-Chlorobenzaldehyde was purified by distillation before use. Spray dried potassium fluoride was purchased from Laporte Industry Co. and Morita Kagaku Kogyo Co.. Polyethylene glycol dimethyl ether having an average molecular weight of 300 and methylnaphthalene were obtained from Daiichi Kogyo Co. and Sumikin Kako Co., respectively.

General procedure for 4-fluorobenzaldehyde (Table 1, run 2)

A 100 ml four-necked flask equipped with a mechanical stirrer, a thermometer, and a water separator was charged with spray dried potassium fluoride (Morita Kagaku Kogyo Co.) (8.7 g, 150 mmol), Ph_4PBr (4.2 g, 10 mmol), tetraethylene glycol dimethyl ether (4.4 g, 20 mmol), 1-chloronaphthalene (20 ml), and toluene (30 ml). The flask was immersed in an oil bath maintained at 140 ^{O}C, and the mixture was stirred to remove toluene azeotropically. After the flask was cooled to 100 ^{O}C, PCAD (14.1 g, 100 mmol) was added in one portion and the whole mixture was stirred for 7 h at 210 ^{O}C under a nitrogen atmosphere. The mixture was then cooled to room temperature and dichloromethane (120 ml) was added. Filtration and concentration followed by distillation gave pure PFAD (8.4 g, 68%) having bp 74-77 ^{O}C/20 mmHg [7]. The IR, NMR, and Mass spectra of this sample were identical with those of authentic PFAD purchased from Aldrich Chemical Co.

Recovery of tetraphenylphosphonium salt

The precipitates were collected by filtration from the cooled residue, washed with diethyl ether, and dried under vacuum to yield 3.4 g (84%) of dry tetraphenylphosphonium

salt. The IR spectrum was identical with that of Ph_4PBr. The analysis of halide by ion chromatography showed a 1:1 mixture of bromide and chloride.

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