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A Convenient Synthesis of Fluorobenzaldehydes by KF/Ph_4PBr/18-Crown-6 Reagent System

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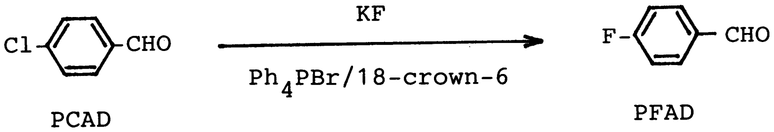
4-Fluorobenzaldehyde was easily synthesized from 4-chlorobenzaldehyde by potassium fluoride in the presence of tetraphenylphosphonium halide plus 18-crown-6 or poly(ethylene glycol) dimethyl ether. Several fluorobenzaldehyde derivatives were similarly prepared from the corresponding chloro-derivatives in good yields.

We report herein an extremely simple and effective procedure for preparing fluorobenzaldehydes based on the solid-liquid phase-transfer catalysis principle. Our method involves the use of tetraphenylphosphonium halide and polyether to convert aromatic chloride into aromatic fluoride by potassium fluoride (KF). When catalytic quantities of tetraphenylphosphonium bromide (Ph_4PBr) and 18-crown-6 or poly(ethylene glycol) dimethyl ether are employed, excellent yields of fluorobenzaldehyde derivatives are readily obtained.



Halogen-exchange fluorination of aromatic halides by metal fluorides is the convenient synthetic way to obtain fluoro compounds in respect of their easy acquisitions and handlings. However, owing to poor solubilities of metal fluorides in organic solvents, the halogen-exchange fluorination with these reagents often requires elevated temperatures in polar solvents such as tetrahydrothiophene 1,1-dioxide (sulfolane), and/or the addition of crown ether or quaternary onium salts as a catalyst.[1-4]

To the best of our knowledge, direct halogen-exchange fluorination of unacti-

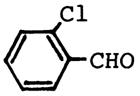
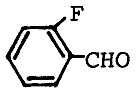
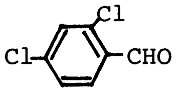
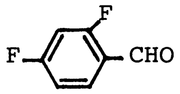
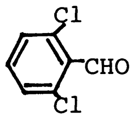
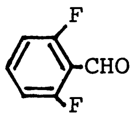
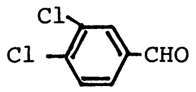
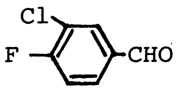
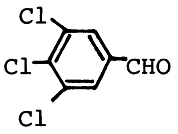
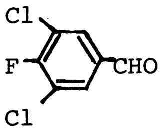
Table 1. Preparation of 4-Fluorobenzaldehyde (PFAD) from 4-Chlorobenzaldehyde (PCAD)a)

Run	Catalystsb) (equiv. to PCAD)	Yield/%c)	
		PFAD	unreacted PCAD
1	Ph_4PBr (0.1) + 18-crown-6 (0.1)	74 (73)	6
2	Ph_4PCl (0.1) + 18-crown-6 (0.1)	70	1
3	Ph_4PBr (0.1)	41	44
4	Ph_4PCl (0.1)	43	21
5	18-crown-6 (0.1)	5	86
6	Ph_4PBr (0.1) + $CH_3O(CH_2CH_2O)_3CH_3$ (0.1)	74	9
7	Ph_4PBr (0.1) + $CH_3O(CH_2CH_2O)_4CH_3$ (0.05)	75	16
8	" + " (0.1)	52	32
9	" + " (0.2)	60	26
10	" + " (0.3)	74	9
11	" + " (0.4)	55	22
12	Ph_4PBr (0.1) + $CH_3O(CH_2CH_2O)_5CH_3$ (0.1)	71	13
13	Ph_4PBr (0.1) + PEG-300Me_2 (0.1)d)	69	13
14	Ph_4PBr (0.1) + $HO(CH_2CH_2O)_4H$ (0.1)	37	23
15	Bu_4PBr (0.1) + 18-crown-6 (0.1)	5	89

a) The reactions were conducted in the same manner as described in the text.
b) Ph_4PBr = tetraphenylphosphonium bromide, Ph_4PCl = tetraphenylphosphonium chloride, Bu_4PBr = tetrabutylphosphonium bromide. c) Yields were determined by GLC analysis using internal standard, and that in parentheses is for isolated product. d) Poly(ethylene glycol) dimethyl ether having average molecular weight of 300.

vated chlorobenzaldehyde derivatives has never been explored by KF with or without phase-transfer catalyst.5) Thus, the reaction of 4-chlorobenzaldehyde (PCAD) with spray dried potassium fluoride in sulfolane was examined by our hands. Treatment of PCAD and 1.5 equiv. of KF in sulfolane at 200 °C for 12.5 h gave only 5% of 4-fluorobenzaldehyde (PFAD). Use of Ph_4PBr4) as a catalyst was next attempted without solvent to avoid the problems associated with use of dipolar aprotic solvents such as decomposition of the solvents in high temperature fluoride reactions and difficulties in product separation and purification.6) A mixture of PCAD and KF in the presence of Ph_4PBr without solvent gave the desired PFAD (41%) and unreacted PCAD (44%) (Table 1, run 3). Though a formation of tarry materials decreased, these reaction system seems not to be applicable to the large scale preparation of PFAD due to rather low yield.

Table 2. Synthesis of Fluorobenzaldehyde Derivatives[a]

Reactant	Product	KF (equiv.)	Time / h	Isolated yield/ %
		1.5	4.5	68[b]
 c)		3	7	49
		2.5	2.5	69
		2	2	66
		1.5	1	75

a) Reaction of 50 mmol of chlorobenzaldehydes with spray dried potassium fluoride (Laporte Ind. LTD.) in the presence of 0.1 equiv. of tetraphenylphosphonium bromide and 0.1 equiv. of 18-crown-6 at 230 °C. b) GLC yield. c) Use of 0.15 equiv. of tetraphenylphosphonium bromide and 0.2 equiv. of 18-crown-6.

We have now found that the fluorination of PCAD with KF can be efficiently achieved by using Ph_4PBr plus 18-crown-6 or poly(ethylene glycol) dimethyl ether catalytic system, to give the desired PFAD in good yield. In a typical experiment (Table 1, run 1), a mixture of 7.0 g (50 mmol) of 4-chlorobenzaldehyde, 4.4 g (75 mmol) of spray dried potassium fluoride (purchased from Laporte Industries LTD.), 2.1 g (5 mmol) of tetraphenylphosphonium bromide, and 1.3 g (5 mmol) of 18-crown-6 was placed in a 50 ml, three-necked, round-bottomed flask equipped with a mechanical stirrer. The flask was immersed in an oil bath maintained at 230 °C, and the mixture was stirred for 4.5 h. The mixture was then cooled to room temperature and diluted with 50 ml of dichloromethane. After filtration and concentration, the residue was distilled to give 4.5 g (73%) of 4-fluorobenzaldehyde having a boiling point of 73-76 °C/22 Torr (lit.,[7] bp 71-73 °C/15 Torr) and identical NMR and Mass spectra with those of an authentic sample. Table 1 summarizes the results obtained for a series of PFAD synthesis. Combination of Ph_4PBr or Ph_4PCl plus 18-crown-6 or poly(ethylene glycol) dimethyl ether had greater activity than phosphonium salt used alone. No desired product was obtained, however, by using large excess of polyether in the presence of Ph_4PBr, and the starting PCAD was almost recovered. Use of another quaternary onium salts instead of tetraphenylphosphonium salt resulted in a decreased yield of PFAD. (Table 1, run 15)

Further evidence of the efficacy of this catalytic reagent system in promoting fluorination of other aromatic aldehydes is provided in Table 2. Ortho- and para-chlorides were smoothly converted to the corresponding fluorides by using 10 mol% of Ph_4PBr and 18-crown-6. A role of crown ether or poly(ethylene glycol) dimethyl ether is presently obscure.

A major synthetic attractiveness of the use of Ph_4PBr-polyether catalytic system is ready availability of starting materials and its experimental simplicity (the use of dangerous hydrogen fluoride is avoided). Efforts are now underway to apply this approach to other fluorination processes.

References

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4) J.H. Clark and D.J. Macquarrie, Tetrahedron Lett., 28, 111 (1987); S. Kumai, Y. Frukawa, M. Sasabe, and M. Matsuo, 11th Symposium of Fluorine Chemistry, Nagoya, October 1986, Abstr., No. 2E07.

5) Reaction of activated chlorobenzaldehyde (3-nitro-4-chlorobenzaldehyde) with KF was already reported: G. Marzolph and H-u. Blank, DE 3111421(1981); Chem. Abstr., 98, 16415 (1983).

6) When a reaction of PCAD with KF in sulfolane in the presence of 0.1 equiv. of Ph_4PBr was employed at 230 °C, a large amount of tarry material was obtained with 49% of PFAD and 5% of unreacted PCAD after 3.5 h.

7) K. Fukui, H. Kitano, T. Osaka, Y. Inamoto, and H. Shirai, Nippon Kagaku Zasshi, 79, 1428 (1958).

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