PRELIMINARY NOTE

A Convenient Synthesis of Fluorobenzoic Acid Esters
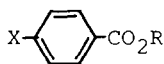via Direct Halogen Exchange

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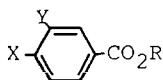Co., Ltd. Fujikawa-cho, Ihara-gun, Shizuoka 421-33 (Japan)

SUMMARY

    The reaction of chlorobenzoic acid esters with potassium
fluoride in the presence of thermally stable phase-transfer
catalysts was investigated.   The yields of fluorinated
products strongly depended on the structure of the substrates
employed.

    Numerous methods for halogen exchange fluorination have
been developed which afford fluoroaromatics in high yields
under mild reaction conditions [1]. We have recently reported
on the convenient synthesis of fluorobenzaldehydes via halogen
exchange with spray-dried potassium fluoride in the presence
of tetraphenylphosphonium salt/ polyether catalytic systems
[2]. During the course of these studies, we became interested
in the fluorination of chlorobenzoic acid esters which have
not yet been reported to participate in halogen exchange
reactions. This reaction would seem to be a new route to
fluorobenzoic acid derivatives, because they are ordinarily
synthesized from the corresponding chlorobenzoyl chlorides or
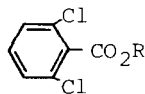chlorobenzonitriles if the halogen exchange method is
applicable.

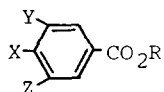$X-\langle\bigcirc\rangle-CO_2R$

1: X=Cl

2: X=F

$X-\langle\bigcirc\rangle-CO_2R$ (Y substituent)

3: X=Y=Cl

4: X=F, Y=Cl

a: R=CH$_2$CH$_3$
b: R=CH(CH$_3$)$_2$
c: R=CH$_2$C(CH$_3$)$_3$

Cl / Cl substituted CO$_2$R

5

$X-\langle\bigcirc\rangle-CO_2R$ (Y, Z substituents)

6: X=Y=Z=Cl

7: X=F, Y=Z=Cl

8: X=Y=F, Z=Cl

9: X=Y=Z=F

$X-\langle\bigcirc\rangle-CO_2R$ (Y, A, Z substituents)
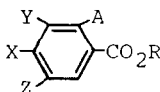
10: X=Y=Z=A=Cl

11: X=F, Y=Z=A=Cl

12: A=F, X=Y=Z=Cl

13: X=A=F, Y=Z=Cl

14: X=Y=A=F, Z=Cl

$TPPB = Ph_4P^+Br^-$

CH$_3$

$DMAPCl = $ (CH$_3$)$_2$N—pyridinium—N$^+$ ... Cl$^-$

CH$_3$ / C$_4$H$_9$ / C$_2$H$_5$
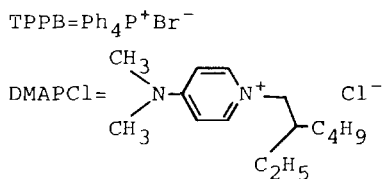
In this context, several chlorobenzoic acid esters were treated with spray-dried potassium fluoride in the presence of thermally stable phase-transfer catalysts (tetraphenyl-phosphonium salts and 4-dialkylaminopyridinium salts) [3]. The results are shown in Tables 1 and 2.

First, ethyl 3,4-dichlorobenzoate (3a), isopropyl 3,4-dichlorobenzoate (3b), and ethyl 3,4,5-trichlorobenzoate (6a) were subjected to attack by 1.4 equivalents of spray-dried potassium fluoride (SD-KF) at 210 °C in the presence of tetraphenylphosphonium bromide (TPPB) and 18-crown-6 (each 0.1 equivalent) without solvent. Such reaction conditions are similar to those employed in the fluorination of chlorobenz-aldehydes [2].

TABLE 1

Fluorination of Chlorobenzoic Acid Esters in the Presence of
Tetraphenylphosphonium Bromide (TPPB) and 18-Crown-6[a]

$$Cl_n\text{—C}_6H_4\text{—}CO_2R \xrightarrow{\text{SD-KF}} F_m\text{—}Cl_{n-m}\text{—C}_6H_4\text{—}CO_2R$$
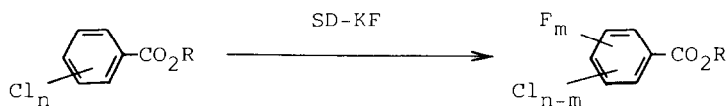
Run	Substrate	KF (equiv)	Temp °C	Time h	Products/% (GC) [Isolated]
1	3a	1.4	210	3	4a [11]
2	3b	1.4	210	2	4b [35]
3	5a	2.5	210	3	---[b]
4	6a	1.3	210	2	7a (69)[44]
					8a (3) [2]
5[c]	10b	2.2	190	5	11b+12b (41)[27]
					13b (31)[25]
					14b (2)

[a] Unless stated otherwise, reactions were carried out in the
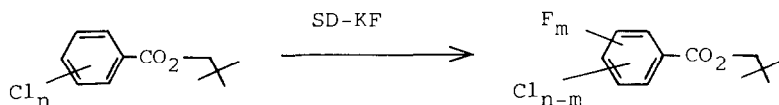presence of TPPB and 18-crown-6 (0.1 equiv of each) without
solvent.

[b] m-Dichlorobenzene was isolated as a sole product (37% yield).

[c] Instead of 18-crown-6, 300 g/mol of sulfolane was added as a
solvent.

In these reactions, the starting chlorobenzates were
found to be almost consumed within 2-3 hours, but the yields
of the desired fluorobenzoates were low. Most of the products
were tarry materials or other unwanted products, which are
presumed to be acid fluorides and 4-alkoxylated benzoates from
the results of GC-MS analysis.

These results suggest that nucleophilic attack of
fluoride anion on the ester carbonyl group causes undesired
side reactions. An effect of side reactions is quite obvious
in the reaction of ethyl 2,6-dichlorobenzoate (5a) (Table 1,
Run 3). In this reaction, no halogen-exchanged product was
observed, but m-dichlorobenzene was isolated as a sole product
via decarbonylation.

TABLE 2

Fluorination of 2,2-Dimethylpropyl Chlorobenzoates[a]

$$Cl_n\text{—} \bigcirc \text{—}CO_2\text{—}\diagup \quad \xrightarrow{\text{SD-KF}} \quad F_m\text{—}Cl_{n-m}\text{—}\bigcirc\text{—}CO_2\text{—}\diagup$$

Run	KF	Temp	Time	Cat.[b]	Materials Recovered	
	(equiv)	°C	h	(equiv)	Substrate/%	Products/%
					(GC)[Isolated]	(GC)[Isolated]
1	1.5	190	5.5	B	1c (83)	2c (10)
2	1.5	210	5.5	B	1c (74)	2c (10)
3	1.5	190	5.5	A	3c (12)	4c (79)[70]
4	1.5	190	5.5	B	3c (6)	4c (91)[70]
5	1.5	190	6	A	6c (12)[10]	7c (84)[76]
						8c (3)
6	1.5	190	6	B	6c (1)[1]	7c (86)[76]
						8c (9)
						9c (2)
7	2.3	190	15	A	10c (0)	11c+12c (7)
						13c (65)[48]
						14c (6)
8	2.3	190	15	B	10c (0)	11c+12c (10)
						13c (63)[46]
						14c (7)

[a] All reactions were carried out in 300 g/mol of sulfolane.
[b] A=TPPB, B=DMAPCl

In an attempt to suppress undesired side-reactions, the halogen-exchange of alkyl chlorobenzoates which have a fairly bulky alkyl (2,2-dimethylpropyl= neopentyl) group was attempted utilizing sulfolane as a solvent in the presence of the catalysts. These results are shown in Table 2. Such a trial seems to be successful for the exclusion of side reactions, but the number of chlorine atoms seems to play an important role in the reactions. For example, the reaction of 2,2-dimethylpropyl 4-chlorobenzoate (1c) gave only 10% of

fluorobenzoates (**2c**) even in the presence of DMAPCl, but most of the starting material was recovered. However, the 3,4-dichloroaryl ester (**3c**) and the 3,4,5-trichloroaryl ester (**6c**) gave 4-fluoroaryl esters in fairly good yields (Table 2, Runs 3-6). On the other hand, the 2,3,4,5-tetrachloro ester (**10c**) gave its 2,4-difluoro analogue (**13c**) in relatively low isolated yield. It is assumed that these reactions were co-accelerated by the substituent effect associated with electronegative chlorine atoms, but fluorinated derivatives of the tetrachloro ester were fairly unstable thermally, which is probably caused by the substitution of several chlorine atoms under the reaction conditions.

In conclusion, we have succeeded in effecting the halogen-exchange fluorination of chlorobenzoic acid esters [4]. The results may offer a new route to the synthesis of certain fluorobenzoic acid derivatives.

1 H. Suzuki, N. Yazawa, Y. Yoshida, O. Furusawa, and Y. Kimura, Bull. Chem. Soc. Jpn., 63 (1990) 2010, and references cited therein.
2 a) Y. Yoshida and Y. Kimura, Chem. Lett., (1988) 1355.
  b) Idem, J. Fluorine Chem., 44 (1989) 291.
3 a) J.H. Clark and D.J. Macquarrie, Tetrahedron Lett., 28 (1987) 111.
  b) G.L. Cantrell, World Patent, WO 87 4148-4150/1987 (to Mallinkrodt Inc.).
4 A part of this work has been published in a form of the patent: Y. Yoshida, Jpn. Kokai Tokkyo Koho, JP64 52 (1989). Similar results were recently appeared in a patent: S. Kumai and R. Seki, Jpn. Kokai Tokkyo Koho, JP2 191 239 (1990). (to Asahi Glass Co.).