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'HALEX' FLUORINATION OF CHLORINATED BENZALDEHYDES AND BENZOYL CHLORIDES

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SUMMARY

Spray-dried potassium fluoride, suspended in sulpholane at 220 °C, converted 2,4- and 2,6-dichlorobenzaldehyde into the corresponding difluoroaldehydes (yields ca. 65%). Small amounts of the mono-substituted products (2-chloro-4-fluoro- + 4-chloro-2-fluoro-benzaldehyde, and 2-chloro-6-fluorobenzaldehyde, respectively) were also produced. Similar treatment of the 3,4-dichloro-analogue gave 3-chloro-4-fluorobenzaldehyde (yield 98%, conversion 68%), but 2- and 4-chlorobenzaldehyde gave very poor yields (ca. 5%) of the 2- and the 4- fluoro-derivatives. 2-Fluoro-, 4-fluoro- and 3-chloro-4-fluoro-benzoyl fluoride were obtained (yields 60-65%) by heating the corresponding chlorobenzoyl chlorides with potassium fluoride in sulpholane.

INTRODUCTION

The recent appearance of publications [1,2] on the synthesis of ring-fluorinated benzaldehydes *via* halogen-exchange between chlorinated benzaldehydes and potassium fluoride, prompts us to report some of our work in this area, initiated several years ago, as part of a programme to find efficient

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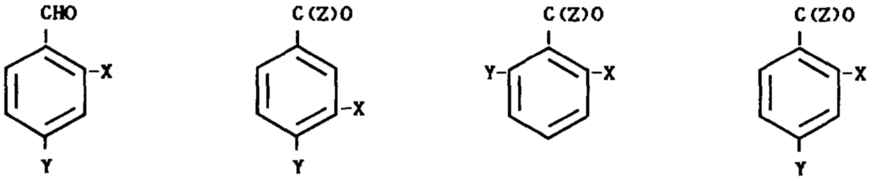
routes to various fluoro-arenes. To make 2,4-difluorobenzaldehyde, for use as an intermediate, standard halogen exchange [3] was attempted on 2,4-dichlorobenzaldehyde , to determine whether the aldehydo-group was sufficiently activating to promote an S_NAr replacement, without being itself attacked by the medium. Recent work [4] had shown that 2-chloro-5-nitro-, 3-chloro-6-nitro- and 4-chloro-3-nitro-benzaldehyde (the nitro-groups being in activating positions, relative to chlorine), were converted efficiently to their fluoro-counterparts in yields of 60-95%. The exchange agent was potassium fluoride suspended in hot dipolar aprotic solvents.

RESULTS AND DISCUSSION

Standard 'Halex' fluorination [3] of five chlorobenzaldehydes (1, 5, 7, 11 and 13; see Scheme), using spray-dried potassium fluoride, slurried in heated (220 °C) sulpholane, was carried out in conventional glass apparatus, in an atmosphere of nitrogen to prevent autoxidation. 2,4-Dichlorobenzaldehyde (1) and KF (molar ratio 2.2:1), stirred together in the minimal practicable volume of solvent for 12 hours, gave 2,4-difluorobenzaldehyde (4, 66 %), and a mixture of the two half-exchanged products, 2-chloro-4-fluoro- and 4-chloro-2-fluoro-benzaldehyde (2 + 3, ratio 7:5; yield 12%). In earlier work [1], a yield of product (4) of 68% was reported.



(1) X=Y=Cl
(2) X=Cl, Y=F
(3) X=F, Y=Cl
(4) X=Y=F

(5) X=Y=Cl, Z=H
(6) X=Cl, Y=F, Z=H
(17) X=Y=Z=Cl
(18) X=Cl, Y=Z=F

(7) X=Y=Cl, Z=H
(8) X=F, Y=Cl, Z=H
(9) X=Y=F, Z=H
(14) X=Y=F, Z=OH
(15) X=Cl, Y=F, Z=OH

(10) X=F, Y=Z=H
(11) X=Cl, Y=Z=H
(12) X=Z=H, Y=F
(13) X=Z=H, Y=Cl
(19) X=Z=Cl, Y=H
(20) X=Z=F, Y=H
(21) X=H, Y=Z=Cl
(22) X=H, Y=Z=F
(23) X=H, Y=Cl, Z=F

Scheme

Re-use of recovered solvent gave marginally better yields (4, 68%; 2+3, 13%), and pre-heating of the sulpholane/KF mixture gave rise to less tar. No advantage was given by the incorporation of tetraphenylphosphonium chloride, in fact the reverse, and the result (yields: 4, 54%; 2+3, traces) compares well with that quoted [2] for the reaction carried out in the presence of tetraphenylphosphonium bromide and 18-crown-6 ether at 230 °C (yield of 4, 49%). Other variations attempted, which also failed to increase the yield of product (4) were as follows:- replacement of sulpholane by diphenyl sulphone, benzonitrile, or 1-methyl-2-pyrrolidone, with or without the addition of toluene and tetramethylammonium chloride [5]; use of potassium fluoride supported on calcium fluoride [6]; ultrasonic activation; catalysis by nickel powder activated with iodine [7]; addition of charcoal.

The best fluorination conditions (KF in sulpholane at 220 °C/1 atm. for 12 h) found for the conversion of (1) to (4) were used for the other cases. With 3,4-dichlorobenzaldehyde (5), only the more activated chlorine was exchanged, giving 3-chloro-4-fluorobenzaldehyde (6) in high yield (98%), based on incomplete conversion (68%) of (5). 2,6-Dichlorobenzaldehyde (7) afforded 2,6-difluoro- (9, yield 64%) and 2-chloro-6-fluoro- benzaldehyde (8, yield 13%). Though both chlorines of substrates (1) and (7) are activated by the aldehyde function, the conversions achieved were good but incomplete.

Very poor yields (5 and 9%, respectively) of 2-fluoro- (10) and of 4-fluoro-benzaldehyde (12) were obtained from the corresponding chloro-analogues (11, 13), which lack any activation from a second halogen. A similar poor conversion of (13) to (12) was reported earlier [2]. However, it was found that, in the absence of solvent, but in the presence of 10% molar proportions of tetraphenylphosphonium bromide, and of either 18-crown-6 ether, or of poly(ethylene glycol) dimethyl ether, greatly improved yields (~73%) of (12) were obtained [2].

The crude reaction products from (1) and (7) were examined in detail by coupled gas chromatography/mass spectrometry, to characterize minor constituents and identify side reactions. Besides exchange products already found (2, 3 and 4 from 1; 8 and 9 from 7), small amounts of dehalogenated, of decarbonylated and of acidic species were detected. For example, from reactions of 2,6-dichlorobenzaldehyde (7), ca. 11·5 wt% of the total product comprised 2-chlorobenzaldehyde (11), 2-fluorobenzaldehyde (10), 2,6-difluorobenzoic acid (14) and 1,3-dichlorobenzene (16), in approximate proportions, respectively, of 13:7:1:2; in a second experiment, 2-chloro-6-fluorobenzoic acid (15) was also detected. Autoxidation by adventitious air during work-up is assumed to have produced the acids (14 and 15). 1,3-Dichlorobenzene could also have arisen by autoxidation of substrate (7) at an earlier stage, followed by decarboxylation of the resultant 2,6-dichlorobenzoic acid; an alternative possibility is direct decarbonylation of (7). 2-Chlorobenzaldehyde (11) was not detected in the starting material (7), and so its presence, and that of the 2-fluoro-analogue (10) may be due to a radical-ion mediated hydrodehalogenation, similar to that believed to occur when 2-nitrohalogeno-arenes undergo halex fluorination with caesium fluoride in DMF [8]. The proportion of (10) relative to (11) is higher than that found from the direct exchange reaction, and this suggests that such a process occurs with both aldehydes (7) and (8) and possibly even with (9).

Thus, the halex fluorination of halogenated benzaldehydes is clearly a useful route to fluoro-aldehydes in many cases. There will be restrictions however because of the relatively low level of activation of nuclear halogen by the CHO group. Instability of this group under the reaction conditions does not seem to be a major limitation, perhaps surprisingly.

Fluorination of Benzoyl Chlorides

3,4-Dichlorobenzoyl chloride (17) afforded 3-chloro-4-fluorobenzoyl fluoride (18), and 2-chlorobenzoyl chloride (19) gave 2-fluorobenzoyl fluoride (20) in yields of 63-65%, when treated under the same conditions as for the aldehydes. By similar treatment of 4-chlorobenzoyl chloride (21), both 4-fluorobenzoyl fluoride (22) (yield 60%) and 4-chlorobenzoyl fluoride (23; 6%) were obtained. Thus, the -C(O)F group promotes greater activation of the halogens in these systems than does the -CHO group, as would be anticipated. The result with acid chloride (21) shows that a chlorocarbonyl group exchanges before nuclear chlorine, again in line with expectation. However, in these media, the possibility of the establishment of equilibria of the type $ArC(O)F + KF \rightleftharpoons ArCF_2OK$ also has to be considered.

Again, therefore, halex reactions of halogenated benzoyl chlorides can offer an easy approach to compounds with a reactive centre already present.

EXPERIMENTAL

General Conditions

Materials Potassium fluoride was commercial spray-dried material (Laporte Industries Plc): it was stored in a dry box. Sulpholane (Aldrich

Chemical Co. Ltd.) had b.p. 285 °C and contained 0.20% w/v of water (Karl-Fischer analysis); it was used as received. 1-Methyl-2-pyrrolidinone, diphenyl sulphone, benzonitrile, calcium fluoride, tetraphenylphosphonium chloride, tetramethylammonium chloride and chlorinated aromatic compounds were also used directly as received from Aldrich. Elemental analysis and ^{1}H nmr and glc/ms spectrometry did not show any impurities in the 2,4- and 2,6-*dichlorobenzaldehyde used.*

Apparatus. Reactions were carried out in a conventional round-bottomed Pyrex flask (250 cm^3), heated by an Isomantle, and fitted with a high-torque mechanical stirrer operating through an oil seal, together with a nitrogen bleed, a thermocouple, and a reflux condenser with calcium chloride guard tube. All reactions were conducted in a very slow stream of nitrogen.

Spectroscopy. Nmr spectra were measured on neat compounds using Perkin-Elmer R32 and R34 instruments. ^{1}H spectra (at 90 or 220 MHz) utilized tetramethylsilane as external reference, and ^{19}F spectra (at 84.6 MHz) had trifluoroacetic acid as external reference. Results are expressed in the order: chemical shift (p.p.m., positive values downfield from ref.), relative intensity of absorption, description of absorption, assignment.

Ir spectra were measured with Perkin-Elmer 197 and 720 spectrophotometers, and mass spectra with a Kratos MS45 (50-70 eV ionization energy).

In all cases, spectroscopic parameters of named products were identical with those of the corresponding authentic specimens: all are well-known.

Halogen Exchange Reactions on Chlorinated Benzaldehyde Substrates

I. *2,4-Dichlorobenzaldehyde (1).* Sulpholane (113 g, 1.1 mole) and 2,4-dichlorobenzaldehyde (1) (43.75 g, 0.25 mole) were added sequentially to potassium fluoride (32.0 g, 0.55 mole). The temperature of the stirred slurry was raised quickly to 220 °C, and maintained there for 12 hours. The colour of the liquid phase became dark brown after ca. 1 hour. The reaction vessel was allowed to cool somewhat, and the contents were then filtered. Distillation of the filtrate through a 15 cm Vigreux column at ca. 40 mmHg pressure afforded fractions (i) - (iii), as detailed below.

Fraction (i) (18.6 g, 0.13 mole) was 2,4-difluorobenzaldehyde (4), b.p. 82 °C/42 mmHg: ir band at 1710 cm^{-1} (C=O): ^{1}H nmr, δ 6.30 (2; complex; 5-, 6-H), 7.10 (1; complex; 3-H), 9.35 (1; singlet; O=C*H*): ^{19}F nmr, δ -22.0 (1; very complex; 4-F), -40.2 (1; very complex; 2-F): m/z 141 (base peak, M-H).

Fraction (ii) (8.25 g) had b.r. 82-165 °C/42 mmHg and was a pale yellow solid: temperature-programmed glc (Pye Unicam GCD; 100-250 °C; 1.5 m x 4 mm glass column; 10% OV-101 on silica; nitrogen carrier gas, 22 psi, 40 cm^3 min^{-1}; injection temp. 250 °C; FID detector temp. 300 °C) and nmr showed the presence of:- (iia) sulpholane (1.03 g); (iib) 2,4-difluorobenzaldehyde (4) (3.01 g, 0.02 mole); (iic) a mixture of 2-chloro-4- (2) and 4-chloro-2- fluorobenzaldehyde (3) (4.2 g, 0.02 mole); (iid) very minor components.

Fraction (iii) (37.5 g) had b.r. 165-200 °C/42 mmHg: it was very complex, but the above techniques showed the presence of products (4) (1.9 g, 14 mmole) and of (2 + 3) (0.6 g, 3.8 mmole).

Total recoveries were:- (4), 23.5 g, 0.165 mole, 66% yield; (2 + 3), 4.8 g, 0.03 mole, 12% yield (2, 7%; 3, 5%).

Other runs carried out are listed below (Table 1) and overleaf (Table 2).

TABLE 1

Experimental Conditions						Materials Recovered		
Run No.	KF /mole	(1) /mole	Sulpholane /mole	Temp. /°C	Time /hr.	Substrate and Products /mole (%) (1)	(4)	(2 + 3)
1	0.55	0.25	1.1	220	12	-	0.165 (66)	0.030 (12)
2	1.1	0.5	2.2	220	13	-	0.316 (66)	0.058 (12)
3{1}	0.55	0.23	1.06	300	24	-	Nothing Tractable	
4	0.54	0.25	1.5{2}	189	12	(92)	0	0
5{1}	0.56	0.25	1.6{2}	290{3}	32	(87)	0	0
6	0.11{4}	0.25	1.05	80{5}	12	(93)	0	0
7	0.11{4}	0.25	1.05	230	12	(57)	0.042 (6)	0
8	0.55{6}	0.25	3.1	220	13	-	0.167 (66)	0.029 (12)
9	0.55{7}	0.25	1.04	220	13	-	0.090 (54)	Traces
10	0.55	0.23	1.1{8}	220	12	-	0.170 (68)	0.036 (13)
11{9}	0.55	0.25	1.1	220	12	-	0.159 (65)	0.049 (10)

{1} Carried out in an autoclave. {2} Benzonitrile was used as the solvent. {3} With nitrogen overpressure (100 psi). {4} Using a mixture of KF (0.11 mole) + CaF_2 (0.44 mole) [cf 6]. {5} In an ultrasonic bath. {6} Using a mixture of KF (0.55 mole) + CaF_2 (0.82 mole) [cf 6]. {7} In the presence of tetraphenylphosphonium chloride (10% by wt.). {8} The sulpholane was recovered from Run 8. {9} The sulpholane/KF mixture was heated under reflux (220 °C/12 hr.), before substrate (1) was added - this resulted in a cleaner reaction system with less tar formation.

TABLE 2

Experimental Conditions						Materials Recovered		
Run No.	KF /mole	(1) /mole	Sulpholane /mole	Temp. /°C	Time /hr.	Substrate and Products /mole (%) (1)	(4)	(2 + 3)
12	0.55	0.25	1.1(1)	210	12	-	0.147 (59)	0.056 (11)
13	0.55	0.25	(2)	130	9	-	0.119 (48)	0.080 (16)
14	0.55	0.23	(2)	130	12	-	0.121 (52)	0.077 (15)
15	0.55(3)	0.25	1.1	220	12	-	Nothing Tractable	
16	0.55(4)	0.23	1.1	220	12	-	0.070 (29)	+ Tar
17	0.55	0.25	0.6(5)	370	6	-	0.137 (55)	0.080 (16)
18	0.55	0.25	0.6(5)	370	12	-	0.139 (56)	0.077 (15)
19	0.55	0.25	(6)	150	12	-	0.119 (48)	0.056 (11)
20	0.55	0.25	(7)	185	12	-	0.137 (55)	0.035 (8)
21(8)	0.55	0.25	0	240	48	(28)	Nothing Tractable	
22(8)	0.57(9)	0.25	0	250	24	-	Nothing Tractable	
23	0.55	0.25	0	350(10)	5	-	0.024 (10)	0
24	0.55	0.25	0	500(11)	5	-	0.040 (18)	0
25	0.25	0.25	0.5	220	12	(29)	0.033 (13)	0.126 (51)

(1) 1-Methyl-2-pyrrolidinone was used as the solvent. (2) The solvent was a mixture of 1-methyl-2-pyrrolidinone (90 g, 0.7 mole) and toluene (37 g, 0.4 mole) containing tetramethylammonium chloride (2·73 g, 0·025 mole) [cf 5]. (3) In the presence of pyrophoric nickel (50 g, 0·85 mole) + a trace of iodine [cf 7]. (4) In the presence of charcoal (1:1, by wt.). (5) Diphenyl sulphone was used as solvent. (6) The solvent was a mixture of sulpholane (60 cm^3) and toluene (60 cm^3) containing tetramethylammonium chloride (2.73 g): (7) As for (6), amounts 85 cm^3, 35 cm^3 and 2.73 g, respectively.
(8) Carried out in an autoclave. (9) As Footnote (7), Table 1.
(10) Using an Isomantle for heating, but without stirring. (11) Using a sand bath for heating, and with stirring.

II. *3,4-Dichlorobenzaldehyde (5).* The reaction, carried out as for general case I above, afforded two fractions:-

Fraction (i) (12.0 g, 0.08 mole), b.r. 91-99 °C/42 mmHg, was 3-chloro-4-fluorobenzaldehyde (6), ^{1}H nmr, δ 7.10 (3; complex; 2-, 5-, 6-H), 9.52 (1; singlet; O=C*H*): ^{19}F nmr, δ -27.0 (complex; 4-F).

Fraction (ii) (33.8 g) had b.r. 100-163 °C/42 mmHg. Temperature-programmed glc and nmr, as before, showed there were present:- (iia) sulpholane

(5.62 g); (iib) 3-chloro-4-fluorobenzaldehyde (6) (14.2 g, 0.09 mole); (iic) 3,4-dichlorobenzaldehyde (5) (14.0 g, 0.08 mole).

The yield of (6) was 98%, based on (5) converted.

III. *2,6-Dichlorobenzaldehyde (7).* Carried out as for case I, there were obtained 2,6-difluorobenzaldehyde (9) (22.9 g, 0.16 mole, 64%) and 2-chloro-6-fluorobenzaldehyde (8) (5.2 g, 0.033 mole, 13%).

In another reaction, the quantities of (7) and KF were 37.2 g and 30.0 g respectively, and the time of heating was 14 hours. The product was then extracted with diethyl ether, the solution filtered and concentrated, and the product distilled to give three fractions, all colourless liquids, (i)-(iii) as follows:-

Fraction (i) (7.0 g) had b.r. 82-96 °C/25 mmHg, and was shown by glc/ms to contain (9) (67%) and (8) (5%). Also present were 2-fluorobenzaldehyde (10) (m/z, 124; 13%); 1,3-dichlorobenzene (16) (m/z, 146, 148, 150; 5%); 2-chlorobenzaldehyde (11) (m/z, 140, 142; 9%); 2,6-difluorobenzoic acid (14) (m/z, 158; 1%).

Fraction (ii) (3.8 g; b.r. 74-92 °C/20 mmHg) contained (glc/ms) (9) (62 %) and (8) (8%); also 2-chlorobenzaldehyde (11) (m/z, 140, 142; 24%); and 2,6-difluorobenzoic acid (14) (m/z, 158; 3%).

Fraction (iii) (13.4 g) with b.r. 110-140 °C/10-7 mmHg contained (glc/ms) (9) (3%) and (8) (22%), together with 2-chlorobenzaldehyde (11) (m/z, 140, 142; 5%), (7) (2%) and sulpholane (64%).

Compound (9) had a ^{19}F nmr peak at δ -38.0 (complex) and m/z, 142 (M): compound (8) had a ^{19}F nmr peak at δ -36.5 (complex) and m/z, 158, 160 (M): 2-fluorobenzaldehyde (10) showed a ^{19}F nmr peak at δ -44.5 (complex).

When the reaction was carried out using sulpholane (57.0 g, 0.47 mole), KF (14.5 g, 0.25 mole) and (7) (43.7 g, 0.25 mole) at 220 °C, for 12 hours, the recoveries were (7) (23%), (8) (49%) and (9) (17%).

IV. *2-Chlorobenzaldehyde (11).* Sulpholane (57.0 g), KF (16.0 g) and the aldehyde (11) (35.1 g) were heated at 220 °C for 12 hours to give recovered (11) (22.4 g, 64%) and 2-fluorobenzaldehyde (10) (4.0 g, 5%).

V. *4-Chlorobenzaldehyde (13).* Carried out as for case IV, this reaction yielded recovered (13) (30.6 g, 87%) and 4-fluorobenzaldehyde (12) (2.8 g, 9%).

VI. *3,4-Dichlorobenzoyl chloride (17).* Compound (17) (52.3 g, 0.25 mole), KF (47.65 g, 0.82 mole) and sulpholane (190 g, 1.57 mole), treated as in case I, afforded 3-chloro-4-fluorobenzoyl fluoride (18) (28.8 g, 0.157 mole, 63%), b.p. 120 °C/42 mmHg,: ^{1}H nmr, δ 6.80 (1; complex; 2-H), 7.50 (2; complex; 5-,6-H): ^{19}F nmr, δ -25.0 (1; complex; 4-F), 95.2 (1; singlet; O=C*F*). An unidentified minor fraction also contained an acid fluoride group.

VII. *2-Chlorobenzoyl chloride (19).* In the same manner, compound (19) (50.0 g, 0.28 mole), KF (46.2 g, 0.57 mole) and sulpholane (214 g, 1.74 mole), gave 2-fluorobenzoyl fluoride (20) (25.8 g, 0.18 mole, 65%), b.p. 105 °C/42 mmHg: ^{19}F nmr, δ -29.3 (1; doublet (39 Hz), each member showing complex splitting; 2-F), 108.0 (1; 39 Hz doublet; O=C*F*).

VIII. *4-Chlorobenzoyl chloride (21).* Carried out as for case VII, this experiment gave; (i) 4-fluorobenzoyl fluoride (22) (23.8 g, 0.17 mole, 60%), b.p. 110 °C/ 42 mmHg: ^{19}F nmr, δ -23.5 (1; complex; 4-F), 94.0 (1; broad singlet; O=C*F*) together with (ii) 4-chlorobenzoyl fluoride (23) 2.66 g, 0.016 mole, 6%): ^{19}F nmr, δ 94.5 (1; broad singlet; O=C*F*).

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