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Tetraphenylphosphonium Bromide Catalyzed Fluorodenitrations and Fluorodesulfonylations. Efficient Syntheses of m-Fluoroaromatic Compounds

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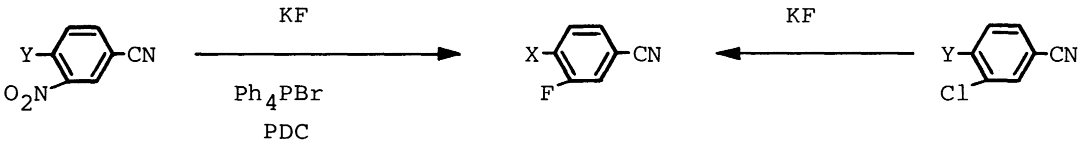
Meta-fluoroaromatic compounds were effectively synthesized from m-nitroaromatic or m-fluorosulfonylaromatic compounds by replacement reaction with potassium fluoride in the presence of a catalytic amount of tetraphenylphosphonium bromide.

In relation to the ongoing project, we required large quantities of 3-fluorobenzonitrile (**1a**) and 3,4-difluorobenzonitrile (**1b**). However, no efficient preparations of **1a** and **1b** have been achieved.[1)] Although the synthesis of fluoroaromatic compounds by halogen-exchange reaction is well known,[2)] the direct preparation of 3-fluorobenzonitrile derivatives from 3-chlorobenzonitrile derivatives has been less studied. Actually, only one process has been reported by recent patent that **1a** was obtained in a 31% GLC yield from 3-chlorobenzonitrile (**2a**).[3)]



3a:Y=H
3b:Y=Cl

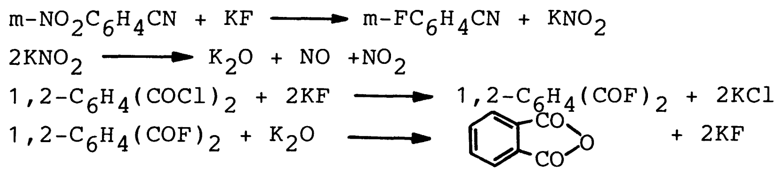
1a:X=H
1b:X=F

2a:Y=H
2b:Y=Cl

We now wish to report a simple and efficient preparative method for m-fluoroaromatic compounds including **1a** and **1b**. Our method is based, conceptually, on halogen-exchange reactions by potassium fluoride (KF), but the leaving group replaced by fluoride is not halide. Meta-fluoroaromatic derivatives prepared in this manner are obtained (1) in good to excellent yields, (2) in relatively simple experimental manners, and (3) without the use of dangerous hydrogen fluoride.

To the best of our knowledge, the results described herein represent the first successful general applications of the halogen-exchange reaction to the synthesis of m-fluoroaromatics.[4)]

Attempted displacement of 3-nitrobenzonitrile (**3a**)(14.8 g, 0.1 mol) by spray dried KF (23.2 g, 0.4 mol) in tetrahydrothiophene 1,1-dioxide (sulfolane, $TMSO_2$) (50 g) at 210 °C, in the absence of a phase-transfer catalyst, resulted in no detectable reaction after 4 h. In contrast, a similar mixture containing 0.1 equiv. of tetraphenylphosphonium bromide (Ph_4PBr)[5)](4.2 g, 0.01 mol) and 1.0 equiv. of phthaloyl chloride (PDC)(20.3 g, 0.1 mol) afforded a 86% isolated yield of **1a**. Similarly, **1b** was obtained from 4-chloro-3-nitrobenzonitrile (**3b**) in 65% yield. Both Ph_4PBr and PDC are essential to get **1a** and **1b** in high yields. PDC seems to be a role of trapping agent of K_2O generated by the decomposition of KNO_2 (Scheme 1).$^{6)}$



$$m\text{-}NO_2C_6H_4CN + KF \longrightarrow m\text{-}FC_6H_4CN + KNO_2$$
$$2KNO_2 \longrightarrow K_2O + NO + NO_2$$
$$1,2\text{-}C_6H_4(COCl)_2 + 2KF \longrightarrow 1,2\text{-}C_6H_4(COF)_2 + 2KCl$$
$$1,2\text{-}C_6H_4(COF)_2 + K_2O \longrightarrow \quad + 2KF$$

Scheme 1.

Actually, the generation of brown gas and the quantitative formation of phthalic anhydride were observed. Tetramethylammonium chloride (Me_4NCl) in place of Ph_4PBr was not efficient as a catalyst.$^{6b)}$ Table 1 summarizes the results obtained for the fluorination reaction of **3a** under various conditions. The potassium fluoride generated in the reaction was not useful for the fluorination reactions. (Table 1, entry 5)

In order to examine the generality of the m-fluorodenitration reaction, the reactions of several m-nitroaromatic derivatives with KF in the presence of Ph_4PBr plus PDC were next examined. The results were shown in Table 2. In all cases the yields compare favorably with those of conventional methods.

Though the developed fluorinations catalyzed by Ph_4PBr are very efficient for the preparation of m-fluoroaromatic compounds, the problems are that PDC is necessary as a trapping agent of K_2O, excess of KF is necessary because PDC reacts with KF to produce phthaloyl fluoride in situ, and some starting nitrocompounds are in danger of explosion.

Thus, we next attempted to use fluorosulfonyl group as a leaving group replaced by fluoride$^{7)}$ to solve these problems. By employing the fluorodesulfonylations catalyzed by Ph_4PBr, m-fluoroaromatic compounds were found to be obtained in fairly good yields. Thus, reaction of 1,3-benzenedisulfonyl fluoride (12.1 g, 50 mmol) and KF (6.5 g, 110 mmol) in $TMSO_2$ (8.5 ml) in the presence of Ph_4PBr (2.1 g, 5 mmol) at 210 °C under reduced pressure (270 mmHg)† for 5 h gave 3-fluorobenzenesulfonyl fluoride (**4**) in 74% yield. The product having a boiling point lower than that of $TMSO_2$ was easily collected as it was distilled from the reaction mixture during the reaction. In this case, addition of PDC did not improve the yield for the fluorination. Without the catalyst, the reaction required more elevated temperature (240 °C) and the yield of **4** was lower. Similar attempts of fluorodesulfonylation reactions were performed as described in Table 3. In all cases, the catalytic effect of Ph_4PBr was revealed.

3,4-Difluorobenzoyl fluoride thus produced seems to be a pivotal position for the synthesis of 3,4-difluoroaromatic congeners such as 3,4-difluorobenzonitrile and 3,4-difluoroaniline, which are useful as intermediates of pharmaceuticals and agrochemicals.

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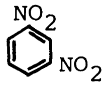
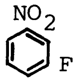
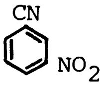
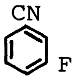
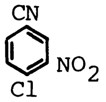
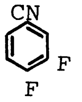
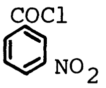
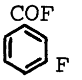
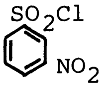
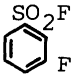
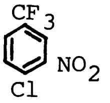
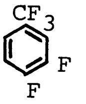
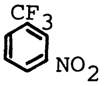
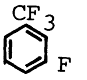
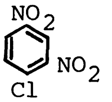
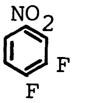
†1 mmHg=133.32 Pa

Table 1. Fluorodenitration of 3-Nitrobenzonitrile

Entry	KF (equiv.)	PDC[b] (equiv.)	Catalyst (0.1 equiv.)	Total reaction time/h	Yield of[c] **1a**/%
1	4.0	1.0	Ph_4PBr	4	86
2	4.0	1.0	Me_4NCl	10	(12)
3	4.0	1.0	none	6	(6)
4	2.0	none	Ph_4PBr	5	(10)
5	2.2	1.0	Ph_4PBr	6	(23)

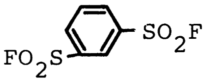
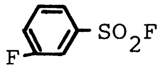
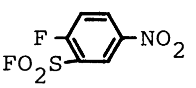
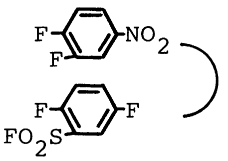
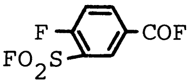
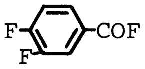
a) All reactions were performed at 150 °C for 2 h, then at 210 °C. b) Phthaloyl chloride c) Isolated yield, yields in parentheses are refer to GLC yield.

Table 2. Ph_4PBr Catalyzed Fluorodenitrations[a]

Substrate	KF (equiv.)	Temp/°C	Time/h	Product	Isolated[b] yield/%	Bp/°C/mmHg or Mp/°C (reported)
	4	180	3		89	78-80/15 (205/760)[c]
	4	210	2		86	81-84/30 (182.6/753)[d]
	5	180	2		65	51-53 (52-54)[e]
	6	210	8		61	56-60/30[f]
	5	210	8		57	78-82/20[g] (78-80/20)[h]
	5	200	3		56	95-98/760 (105/760)[i]
	4	210	8		53	100-103/760 (101/760)[j]
	5	190	6		46	80-85/15[k] (76-80/11)[l]

a) Reaction of substrate (0.1 mol) with spray dried KF in the presence of PDC (0.1 mol) and Ph_4PBr (0.01 mol) in sulfolane (50 g) at 150 °C for 2 h then at appropriate temperature. b) All samples gave satisfactory IR and Mass spectra. c) E.D. Bergmann, S. Berkovic, and R. Ikan, J. Am. Chem. Soc., 78, 6037 (1956). d) F. Swarts, J. Chim. Phys., 20, 74 (1923). e) The Aldrich Fine Chemicals Catalog Handbook, p.539 (1988). f) This sample was identified as diethylamido derivative by comparison with the authentic sample which was prepared from 3-fluorobenzoyl chloride. g)Along with 3-fluoronitrobenzene in 7% yield. h) Ref. 7 i) W.J. Feast, W.K.R. Musgrave, and R.G. Weston, J. Chem. Soc., C, 1971, 1547. j) L.V. Cherry, M.E. Hobbs, and H.A. Strobel, J. Phys. Chem., 61, 465 (1957). k) Along with 2,5-difluoronitrobenzene in 3% yield. l) Ref. 4a.

Table 3. Ph_4PBr Catalyzed Fluorodesulfonylations[a)]

Substrate	Temp °C	Catalyst (0.1 equiv.)	Product	Isolated yield/%	Bp/°C/mmHg (reported)
	210	Ph_4PBr		74	87/20 (92-101/20)[b)]
"	240	none	"	54	
"	240	none	"	44[c)]	
	210	Ph_4PBr		49[d)]	86-88/20 (76-80/11)[e)]
"	220	none	"	13[c,d)]	
	210	Ph_4PBr		45	74/75[f)]

a) Reaction of substrate (50 mmol) with KF (110 mmol) in the presence of Ph_4PBr (5 mmol) in sulfolane (8.5 ml) for 5 h under reduced pressure (270-300 mmHg): during which time the products were distilled out along with the $TMSO_2$. After washing with water, subsequent distillation resulted in the pure products. b) Ref. 7 c) Without distilling out product during fluorination reaction. d) A 7:1 mixture of 3,4-difluoronitrobenzene and 2,5-difluorobenzenesulfonyl fluoride (GC-MS: m/e 159 and 196) was obtained together. Both boiling points were in the same range. e) Ref. 4a. f) Calcd for $C_7H_3F_3O$: m/z 160.0136, Found: m/z 160.0135. The acid fluoride was also identified as a known 3,4-difluorobenzoic acid by hydrolysis: mp 120 °C (lit.,[8)] mp 119.2-120.1 °C).

References

1) **1a** and **1b** could be elaborated by multi-step synthesis from the fluorotoluene derivatives which were prepared by Balz-Schiemann reactions: cf. H. Hopff and G. Valkanas, J. Org. Chem., 27, 2923 (1962).

2) N. Ishikawa, Yuki Gosei Kagaku Kyokai Shi, 25, 808 (1967); N. Ishikawa and T. Kitazume, ibid., 34, 173 (1976); Y. Kimura, ibid., 47, 258 (1989).

3) S. Kumai and R. Seki, Japan Kokai Tokkyo Koho, JP 63-203636 (1988).

4) Fluorodenitrations of 1,3-dinitrobenzene derivatives without catalyst have been reported to give m-fluoronitrobenzene derivatives: a) G.C. Finger and C.W. Cruse, J. Am. Chem. Soc., 78, 6034 (1956); b) G. Bartoli, A. Latrofa, F. Naso, and P.E. Todesca, J. Chem. Soc., Perkin Trans 1, 1972, 2671; c) F. Effenberger and W. Streicher, Ger. Offen, DE 3400418 (1985); Chem. Abstr., 104, 148476w (1986).

5) J.H. Clark and D.J. Marquarrie, Tetrahedron Lett., 28, 111 (1987); Y. Yoshida and Y. Kimura, Chem. Lett., 1988, 1355.

6) a) T. Tanabe, Nippon Kagaku Kaishi, 1985, 2199; b) S. Kumai, R. Seki, Y. Furukawa, and M. Matsuo, Reports Res. Lab. Asahi Glass Co., 35, 153 (1985).

7) The reaction of 1,3-benzenedisulfonyl fluoride derivatives with KF has recently reported: M.V.D. Puy, J. Org., Chem., 53, 4398 (1988).

8) J.T. Minor and C.A. Vanderwerf, J. Org. Chem., 17, 1425 (1952).

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