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REGIOSPECIFIC AROMATIC FLUORODEMETALLATION OF GROUP IVb METALLOARENES USING ELEMENTAL FLUORINE OR ACETYL HYPOFLUORITE

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SUMMARY

The reactions of fluorine and acetyl hypofluorite with trimethylaryltin, -germanium, and -silicon compounds were studied using fluorine-18 ($T_{1/2}$ = 110 min) as a radiochemical tracer. The fluorodemetallation of phenyl derivatives by sub-stoichiometric F_2 to yield fluorobenzene was almost independent of temperature (-78^{0} to 22^{0}C), reaction time (2 to 200 min) and substrate concentration (2 to 150 mM). The reactions of both fluorination agents were not affected by perhalogenated methanes as solvents, but completely suppressed in solvents with active hydrogens. In a series of p-substituted phenyl derivatives (CH_3O-, CH_3-, H-, F-, Br-, CF_3-, O_2N-), a decrease in the fluorodemetallation yield was observed in the order Sn > Ge > Si, and with rings containing electron-withdrawing groups. The reactivity of CH_3CO_2F with stannylated arenes was equal to that of F_2, but much lower than that of F_2 when arylgermanium or -silicon derivatives were used. These findings are in agreement with a substitution mechanism involving a σ-complex. The only side-products which formed from the corresponding metallated anisyl- and toluyl-compounds were 2-fluoroanisole (< 16%) and benzylfluoride (< 5.5%). No direct hydrogen substitution was observed in the other substrates investigated. The high regiospecific fluorination yields obtained make aromatic fluorination of group IVb metallated arenes (especially of tin) a very attractive preparative fluorination and radiolabelling method.

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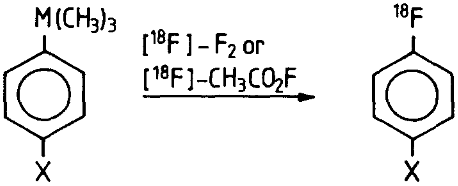
INTRODUCTION

Aromatic halodemetallation reactions have been known for a long time (for a review see [1]), but are not commonly used in organic chemistry. Recently, interest in the application of metalloarenes for the labelling of aromatic compounds, especially with radiobromine and radioiodine (for a review see [2]), has arisen. These demetallation reactions enable the site-specific substitution of a labile metal moiety with high yield, which makes it ideally suited for mild and effective halogenation with short-lived radionuclides.

The positron-emitting fluorine-18 ($T_{1/2}$ = 110 min) has ideal nuclear properties for use as a label of radiopharmaceuticals for positron emission tomography. Labelling with this short-lived radionuclide requires rapid and effective reaction conditions for often sensitive substrate molecules. Fluorodemetallation reactions have been employed for aromatic fluorination and radiofluorination, and its usefulness as a labelling method has been demonstrated using aromatic compounds containing tin, silicon, germanium, lead, and mercury substituents as precursors [3-14].

This paper reports a systematic study of the influence of the metal displaced and of aromatic substituents on the aromatic fluorodemetallation of aryltrimethyl group IVb organometallics using elemental fluorine or acetylhypofluorite (Scheme 1). Besides finding optimal fluorination conditions, side reactions which result from the high reactivity of fluorine are considered. As carrier-added ^{18}F was used in these experiments,



X = OCH_3, CH_3, H, F, Br, CF_3, NO_2

M = Si, Ge, Sn

SCHEME 1

the results are pertinent to preparative organic chemistry as well as to the radiosynthesis of medium specific activity (< 2 Ci/mmol) radiopharmaceuticals. Moreover, use of radioactive fluorine facilitates measurement of reaction products at the micromolar level by means of radioanalytical methods.

RESULTS AND DISCUSSION

Reaction parameters

In initial experiments, 40 µmol (8 mM) trimethylphenyltin or -silicon were reacted with $[^{18}F]$-F_2 in $CFCl_3$ at -78°C. Constant yields of 64 ± 7% for Sn and 23 ± 4% for Si were found over a substrate / F_2 molar concentration ratio of 2-10. Below 1 µmol of F_2, the yields were negligible, probably due to reaction with impurities in the reaction solution. A small increase in the fluorination yield of 8% was found for the silicon analogue when a trimethylphenylsilicon / F_2 molar concentration ratio of 160 was used, but no such effect was observed for the more reactive tin derivative. Increasing the temperature of the reaction solution from -78°C to 0°C or 22°C had negligible effects on the fluorodemetallation yields. The reaction yield of fluorobenzene was also unaffected by the time lapse between the F_2/Ne purging of the reaction solution and its extraction with chloroform / aqueous Na_2SO_3 (2 to 200 min).

TABLE 1

Effect of solvent on the chemical yields of fluorodestannylation of trimethylphenyltin by $[^{18}F]$-F_2 or $[^{18}F]$-CH_3CO_2F[a]

Solvent	$CFCl_3$	$CFCl_3$	CCl_4	CH_2Cl_2
Temperature	-78°C	0°C	0°C	0°C
$[^{18}F]$-F_2	64.4±6.7	66.2±4.2	62.4±0.8	18.2±2.1
$[^{18}F]$-CH_3CO_2F	28.5±1.3	68.2±5.2	65.5±5.5	14.5±1.8

[a] Reaction conditions: 40 µmol substrate in 5 ml of solvent; substrate/F_2 (CH_3CO_2F) molar ratio equals 5 to 8

The lack of strong influence of reaction time, temperature, and reagent concentration on the fluorodestannylation and -desilylation indicate the high reactivity of elemental fluorine. Acetyl hypofluorite [15] is a milder reagent than F_2, and has been used for monofluorination of aromatic rings via fluorodeprotonation [16] and for fluorodemetallation in acidic media [5-7,10-14]. The data given in Table 1 compare the reactivity of elemental fluorine or acetyl hypofluorite with trimethylphenyltin in halogenated methane solvents. It can be seen that the chemical fluorination yields from F_2 are not affected by changes in solvent polarity or temperature. Acetyl hypofluorite, on the other hand, exhibits a low reactivity in $CFCl_3$ at low temperatures, which corresponds to the reduced reactivity of this fluoroderivative [15,16]. The yields from acetyl hypofluorite at elevated temperatures are equal in $CFCl_3$ and CCl_4 and comparable to those obtained with F_2. Although it was possible to achieve fluorination with reduced yields using polar, hydrogen-containing methylene chloride, fluorodestannylation did not occur in solvents containing methyl groups such as dimethylsulfoxide (DMSO), hexamethylphosphoric acid triamide (HMPA), N,N'-dimethyl-N,N'-propyleneurea (DMPU), and acetonitrile. Correspondingly, the major part of fluorine activity was found in the inorganic phase.

Metal and substituent effect

Para-substituted phenyl derivatives of trimethyltin, -germanium, and -silicon were reacted in $CFCl_3$ with $[^{18}F]$-F_2 at -78°C and with $[^{18}F]$-CH_3CO_2F at 0°C. The yields of para-substituted aryl fluorides obtained are summarized in Table 2. Three general trends are prevalent: i) for a given substituent, all fluorodemetallation yields decrease in the order Sn > Ge > Si; ii) the reactivity of F_2 and CH_3CO_2F is affected by aromatic substituents; and iii) fluorodemetallation yields are equal using fluorine or acetyl hypofluorite with stannylated arenes but are much smaller when CH_3CO_2F is used with germylated- or silylated arenes.

The decrease in the fluorination yield by a factor of approximately three when going from the stannylated to the silylated substrates corresponds to the increase of carbon-metal bond energies (Sn, 257 kJ/mol; Ge, 308 kJ/mol; Si, 352 kJ/mol) [17], and the decrease in carbon-metal bond lengths (Sn, 1.54 Å; Ge, 1.36 Å; Si, 1.31 Å) [18,19], factors which disfavour aromatic demetallation. A similar trend has been found and discussed for bromo- and iododemetallation [20].

TABLE 2

Effect of substituent and metal on the fluorodemetallation yields of para-substituted trimethylaryl group IVb organometallics ($p\text{-}X\text{-}C_6H_4\text{-}M(CH_3)_3$) using molecular fluorine or acetyl hypofluorite[a]

X	M	% Chemical Yield[b] Sn	Ge	Si
OCH_3		70.4 ± 6.6 (66.0 ± 4.3)	35.4 ± 1.4	19.8 ± 3.0
CH_3		78.4 ± 6.4	40.6 ± 5.8 (16.4 ± 1.8)	22.4 ± 4.0 (9.1 ± 1.1)
F		73.8 ± 6.8	55.8 ± 3.6	30.4 ± 3.2
H		64.4 ± 7.0 (68.2 ± 5.7	40.4 ± 4.0 (8.5 ± 0.5)	23.0 ± 4.0 (3.5 ± 0.3)
Br		34.2 ± 3.4	24.8 ± 0.8	10.2 ± 0.6
CF_3		35.0 ± 2.8 (36.3 ± 1.6)	10.4 ± 1.6	2.4 ± 0.5

[a] Reaction conditions: 6 to 8 mM solution of substrate in $CFCl_3$; 3 to 5 μmol fluorination reagent; temperature = -78°C for F_2, 0°C for CH_3CO_2F

[b] Values in parentheses are for acetyl hypofluorite, other values are for fluorine

For a given trimethylmetal substituent, the fluorination yields are dependent on the nature of the second substituent on the aromatic ring. Whereas almost no yield was observed with para-nitro derivatives (not shown in Table 2), the reactivity increases as electron-withdrawing substituents (NO_2, CF_3, Br) are replaced by non-electron with-drawing groups (H,F). With the electron-donating groups (CH_3, OCH_3), however, no further increase in yield, but rather a decrease in the fluorination yields with the less reactive organometallics is found. Although a correlation of yields with Brown's σ^+ substituent constants [21] for electrophilic substitution was not possible, from the general electronic influence of substituents on the reactivity, it can be concluded that the fluorodemetallation reactions are electrophilic in nature. The unexpectedly low fluorination yields obtained with electron-donating substituents (CH_3, OCH_3) are probably due to hydrogen abstracting side reactions. Due to the lower reactivity of silylated arenes, side reactions play a dominant role with these substrates.

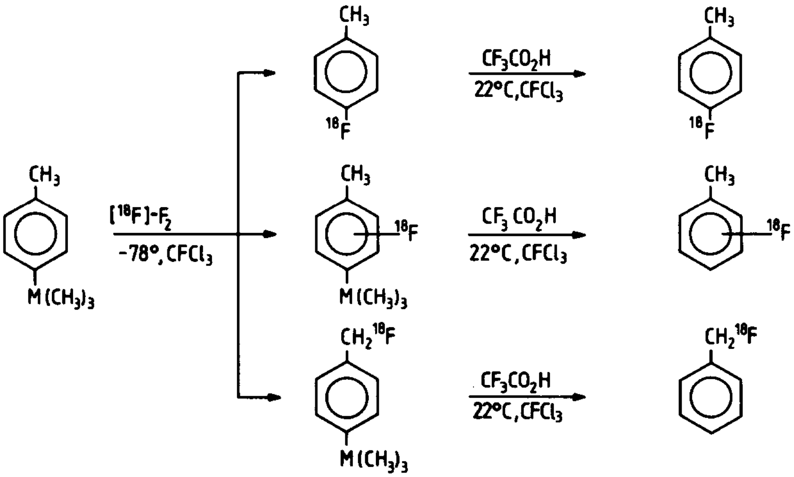
The fluorodestannylation yields from acetyl hypofluorite in $CFCl_3$ at 0^oC are not significantly different from those obtained using elemental fluorine at -78^oC. However, the decrease in fluorodemetallation yields from ca. 70% for trimethylphenyltin to < 5% for trimethylphenylsilicon is much more dramatic for acetyl hypofluorite than for elemental fluorine (see Table 2). Acetyl hypofluorite is less reactive than elemental fluorine as indicated by the negligible aromatic fluorination yields obtained using aromatic systems nonactivated toward electrophilic substitution [16,22].

The major parameter determining the fluorodemetallation yields seems to be the metal which is displaced rather than the para-substituent, since the relative yields for displacement of tin, germanium, or silicon is generally independent of ring substituents (except for the CF_3-substituent). The secondary yield-altering effect of aromatic substituents may be due to stabilization/destabilization of a σ-complex intermediate hypothesized for electrophilic aromatic demetallation [20,23].

The data in Table 2 indicate that the stannylated arenes are superior to the other metallated compounds for fluorodemetallation when fluorine or acetyl hypofluorite is used. This is also true when the data in the literature is compared for the reactions of acetyl hypofluorite with tri-n-butyltin compounds [6,7], O-acetyl- or chloro-mercury compounds [14], or arylpentafluorosilicates [12]. In cases where silicon or germanium derivatives are preferable for synthetic or stability reasons, elemental fluorine is the better fluorination agent. The yields given in previous reports for the destannylation and desilylation reactions using F_2 [6,7,9] are consistent with the findings in the present study. They deviate considerably, however, for the yields obtained from halogen-substituted phenyltin compounds [6,7]. The > 95% fluorodestannylation yields reported correspond to the total organic yields found here.

Side-product formation

The total organic fluorine yield was in most cases considerably higher than the aromatic substitution yield. As discussed above, fluorination side reactions may occur at sites of the substrate molecule other than that occupied by the metal substituent (Scheme 2). Minimizing the product spectrum has the practical advantage of making the purification of the desired product easier. Elemental fluorine is known to react vigorously with aromatic derivatives [1,24] and even in diluted states polyfluorination and polymer formation are induced [25] which may involve multiple overlapping mechanisms [26]. Even acetyl hypofluorite induces direct fluorodeprotonation in arenes [16,22], and it has been demonstrated that $[^{18}F]$-F_2 and $[^{18}F]$-CH_3CO_2F can be used for radiofluorination of activated arenes [27,28].



SCHEME 2

To analyze for possible fluorodeprotonation products (2- and 3-fluoroderivatives), the reaction mixture was treated with trifluoroacetic acid to form disubstituted products via cleavage of the carbon-metal bond. Gas chromatography was then used to detect the various aromatic fluoro isomers. This analytical sequence is illustrated for the toluyl derivatives in Scheme 2, where the ortho- and meta-isomers and benzyl fluorides are formed following protolysis, in addition to the desired para-fluorinated demetallation product. Preceeding the radiofluorination experiment, the protolysis half-times were determined by means of GC analysis. Completion of reaction was a matter of a few minutes for tin derivatives in contrast to, for example, 130 ± 10 minutes for trimethyltoluylsilicon. This reflects the high reactivity of the stannylated compounds toward electrophilic decomposition (cf. [29]). Special attention was given to the benzyl fluorides due to their possible acid-catalyzed hydrolysis [30]. However, decomposition was not observed under the almost anhydrous protolysis conditions (CF_3CO_2H in $CFCl_3$).

TABLE 3

Chemical yields of products formed from fluorodemetallation reactions on anisyl- and toluyltrimethyl metal compounds and subsequent treatment with CF_3CO_2H (cf. Scheme 2)

Substrate	Reaction Condition	4-Fluoro-anisole	2-Fluoro-anisole	2-F-, 4-$(CH_3)_3$M-Anisole
$(CH_3)_3SnC_6H_4OCH_3$	F_2, $CFCl_3$, -78°C	70.4±6.6	11.6±2.2	-
			6.8±0.6[a]	3.0±1[a]
	CH_3CO_2F,$CFCl_3$, 0°C	66.0±4.3	6.0±0.4	-
	CH_3CO_2F,CH_2Cl_2, 0°C	38.8±2.1	7.4±0.6	-
$(CH_3)_3GeC_6H_4OCH_3$	F_2, $CFCl_3$, -78°C	35.4±1.4	16.0±1.0	-
			3.8±0.2[a]	10.6±0.6[a]
$(CH_3)_3SiC_6H_4OCH_3$	F_2, $CFCl_3$, -78°C	19.8±3.0	13.0±1.0	-
			0.6±0.2[a]	13.0±0.8[a]
		4-Fluoro-toluene	α-Fluoro-toluene	
$(CH_3)_3SnC_6H_4CH_3$	F_2, $CFCl_3$, -78°C	78.4±6.4	5.6±0.6	
$(CH_3)_3GeC_6H_4CH_3$		40.6±5.8	4.4±0.8	
$(CH_3)_3SiC_6H_4CH_3$		22.4±4.0	3.2±0.4	

[a] Yields of substitution products obtained without protolytic cleavage of carbon-metal bonds.

No fluorodeprotonation products, however, could be detected, except for the anisyl- and toluyl-metallated derivatives. Their fluorodemetallation and fluorodeprotonation yields obtained under various reaction conditions are summarized in Table 3. Ortho fluorination occurs with all three metallated anisyl-derivatives in $CFCl_3$ at -78°C with an almost identical yield of 12-16%. The results obtained after protolysis of the metal-carbon bond are in close agreement with those of the analysis of primary reaction products (cf. Scheme 2). The reaction of acetyl hypofluorite in $CFCl_3$ and CH_2Cl_2 at 0°C also gives a 6 to 7% ortho substitution yield in spite of its lower reactivity. The absolute ortho yield from elemental fluorine did not change when the substrate / F_2 ratio was increased from 1 : 1 to 30 : 1, indicating a high specificity of F_2 for this position. The increasing yield of 4-fluoroanisole relative to 2-F, 4-trimethylmetallated anisole as Si < Ge < Sn reflects the relative lability of the aromatic metal moiety to fluorine displacement in competition with the 1,2 addition-elimination pathway hypothesized for ortho-fluorodeprotonation [22].

In the case of toluyl derivatives no ring deprotonation occurs, and only benzyl fluoride is formed, as shown in Table 3. The yields increase from the silylated to the stannylated analogue. The side-product yields are very small and cannot account for the 'missing' organic products (difference between total organic yield and identified fluorination products). Since the activation energy for abstraction of hydrogen from benzylic positions by fluorine radicals is almost zero [31], the assumption that the fluorination reactions in these systems are of heteropolar nature seems justified. The 'missing' organic products therefore are probably formed by fluorination of the solvent molecules or by fluorination reactions with the trimethylmetal group instead of the aromatic ring.

EXPERIMENTAL

Reagents

The aromatic haloarenes used as reference compounds for gas chromatography or for the synthesis of the aryltrimethyl organometallics were purchased with 98-99% purity from Fluka (West Berlin) or EGA Chemie (Steinheim, FRG). The para-substituted aryltrimethylsilicon, -germanium, and -tin compounds were synthesized via the Grignard derivative of the corresponding brominated arene, purified, and chemically characterized [32].

The precursor for the three 2-fluoro-4-trimethylmetallated anisyl derivatives used as GC standards were obtained by bromination of 2-fluoroanisole using bromine and iron catalyst at 90°C [33]. Benzylfluoride was prepared from benzylbromide (Merck, Darmstadt, FRG) using potassium fluoride and dibenzo-18-crown-6 [34]. The latter two compounds were identified by boiling point and ^{1}H-NMR.

Freon-11 ($CFCl_3$) was purchased from Matheson (Heusenstamm, FRG), distilled, and stored over 4 Å molecular sieves. All other solvents used in this study were of analytical grade and were obtained from Merck. The $KOAc(HOAc)_{1.5}$ complex for the production of acetyl hypofluorite was prepared as described [35].

Production of fluorine-18 and fluorination procedure

The $[^{18}F]$-F_2 was produced via the $^{20}Ne(d,\alpha)^{18}F$ reaction in a nickel-plated target containing 18 bars of 0.25% F_2 in neon (Matheson) using a 14 MeV (25 µA) deuteron beam from the Jülich CV-28 compact cyclotron. A target system and a stainless steel manifold for handling the inactive and radioactive fluorine gas was used as described in the literature [4,36]. After irradiation, the target chamber was expanded with a flow of 20 ml/min in fractions into different reaction vessels. The amount of fluorine released per given volume was determined by absorption in aqueous KI/K_2CO_3 and measurement of fluoride concentration with an ionsensitive glass electrode [37].

In a typical experiment, the narrow 10 ml gas-tight reaction vessel contained 10 µl (30-40 µmol) of the trimethyl-metallated arene in 5 ml of solvent. Cooling was performed by methanol/dry ice (-78°C) or ice-water (0°C). No special precaution was taken to exclude moisture. Unless otherwise noted, 1-5 µmol $[^{18}F]$-F_2 was administered to the reaction solution by teflon tubing to give an 8-30 fold excess of substrate. To produce acetyl hypofluorite, an equal amount of $[^{18}F]$-F_2 was passed through a 0.4 x 5 cm glass tube filled with $KOAc(HOAc)_{1.5}$ and the $[^{18}F]$-CH_3CO_2F formed was immediately purged into the reaction solution [35]. Between the reaction vessel and the exhaust a sodalime trap and a molecular sieve (10 Å) trap were placed to absorb unreacted fluorine activity. About 80% of both the fluorine species was absorbed in the reaction solution in the described set-up.

Analysis

10 Minutes after the reaction (purging of gas) was finished, 5 ml of 3% Na_2SO_3 and 5 ml of chloroform containing 1 μl/ml of the expected products as reference standards for GC were added. After extraction, the organic layer was separated, dried over $CaCl_2$, and an aliquot (10-50 μl) analyzed on a Hewlett-Packard 7620-A gas chromatograph. The aromatic isomers of the fluoroarenes were separated on 4000 x 4 mm glass columns containing either 6% Bentone-38 and 20% silicon oil DC-200 or Igepal CO-880 on Chromosorb W-AW-DMCS (60-80 mesh) [38,39]. For radioactivity assay individual gas chromatographic fractions were absorbed on charcoal by a discontinuous technique [40] and counted in a well-type γ-scintillation counter. The radiochemical yields were calculated by comparison of the radioactivity of GC fractions with that from aliquots of the organic and inorganic phases.

For protolysis of the organometallic compounds, 100-200 μl of trifluoroacetic acid was added to the reaction solution preceeding extraction with chloroform / water (cf. Scheme 2). The rate of protolysis was determined by measuring the TCD signal of the metallated compound and the signal of the corresponding monosubstituted benzene formed after fixed reaction time intervals.

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