Fluorination and Fluorodemercuration of Aromatic Compounds with Acetyl Hypofluorite

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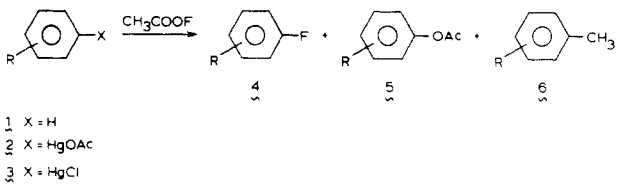
There is an increasing interest in fluorinated aromatic compounds especially from a pharmaceutical point of view.[1] However, problems regarding the introduction of fluorine into organic molecules differ considerably from those concerning other halogen atoms. Only a few practical methods are available for the controlled regiospecific introduction of fluorine into aromatic compounds[2] since most fluorinating agents suffer from over-reactivity. Recently, cesium fluoroxysulfate[3] has been suggested as an alternative to acetyl hypofluorite[4] for which the reactions have to be carried out at low temperatures. However, acetyl hypofluorite can conveniently be prepared at room temperature either in acetic acid[5] or by a gas-solid-phase reaction[6] and is as such a very easily handled fluorinating agent. We now report our investigations on the use of acetyl hypofluorite in acetic acid for the regiocontrolled monofluorination of aromatic compounds, starting from the corresponding mercurated derivatives.[7] On the basis of the observed byproducts, a one-electron transfer mechanism leading to an intermediate radical-cation is proposed which might contribute to a better understanding of electrophilic fluorination, a subject of considerable debate and controversy.[4,8]

Results and Discussion

Halogenation through mercury compounds is a well-known route to the regiospecific synthesis of chloro, bromo, iodo, and astato compounds.[9,10] In analogy, fluorodemercuration was initially performed with molecular fluorine in acetic acid. However, the yields were too low to be of synthetic interest. Better results were obtained by using acetyl hypofluorite as fluorodemercurating agent (Table I). With activating substituents the yield was somewhat lower than in the reaction with the non-mercurated analogues, but isomerically pure compounds were obtained. Interestingly, the results obtained for mercurated benzene and toluene indicate suppression of unwanted side reactions, since their yield drastically increased. However, for the compounds with R = Cl, COOH, or NO_2 low yields were found, and it can, therefore, be concluded that this fluorodemercuration is not applicable to aromatics with deactivating groups.

Since it has been reported that reaction of acetyl hypofluorite with phenol in freon mainly results in oxidation products,[11] the fact that both **1** and **3** (R = OH) (Scheme I) give good yields must be due to the use of acetic acid as solvent. In contrast, acetic acid was not capable to prevent oxidation of aniline, *N,N*-dimethylaniline, and their para-mercurated analogues, because apart from low yields strongly colored solutions were obtained. Another effect of acetic acid as solvent is the lower "ortho effect"; for anisole and acetanilide ortho/para ratios of 3 and 2 were obtained, whereas in freon ortho/para ratios of 9 and 7 were found, respectively.[11] Presumably, interaction of

Scheme I



acetyl hypofluorite with the substituent R (OCH_3, NHAc) is decreased in a polar solvent such as acetic acid.

Although alkylmercury compounds are more difficult to synthesize than arylmercury compounds,[9b] it was thought to be of interest if acetyl hypofluorite upon reaction with compounds containing an aliphatic carbon–mercury bond would give the corresponding fluoro compound. Indeed, with dibenzylmercury as a model substrate, benzyl fluoride was obtained in a yield of 46%. Moreover, this illustrates once more that the ligand attached to the mercury atom is not a crucial factor as was already shown by the lack of difference in reaction products between phenylmercury acetate (**2**, R = H) and the chloride **3** (R = H).

The yields of the fluorodemercuration of mercurated toluenes by acetyl hypofluorite as a function of the reaction time are given in Table II. The reaction was stopped by the addition of anisole which is known to react within seconds. From these results, it can be concluded that after 5 min the reaction is almost completed but also that there is an acetyl hypofluorite consuming side reaction. The same experiments performed with mercurated chloro- and nitrobenzene showed that although barely any fluorodemercuration product was obtained, all the acetyl hypofluorite had disappeared within 5 min. The reactions of **1**, **2**, and **3** with acetyl hypofluorite in acetic acid were, therefore, analyzed by GCMS (Table I). These analyses revealed that apart from fluoro compounds **4** and some high-boiling dimers, two important classes of compounds were also formed: the corresponding acetoxy and methyl derivatives **5** and **6**. While for R = OCH_3 **5** and **6** were present in minor amounts, it appeared that for R = Cl **5**

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Scheme II

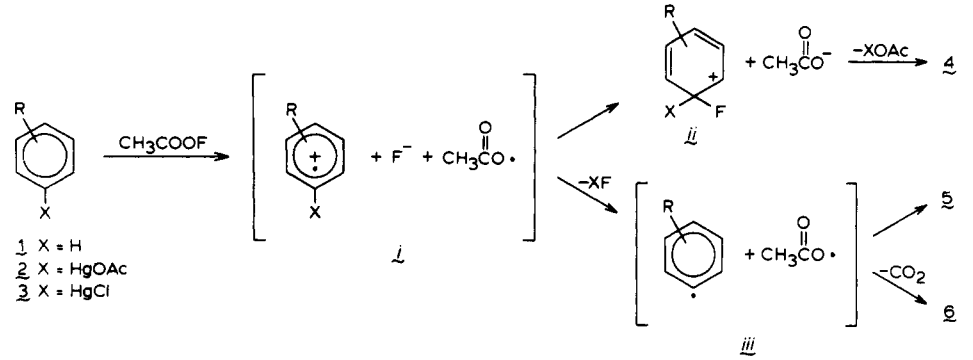

Table I. Reaction Products Formed according to Scheme I by Using CH_3COOF in CH_3COOH

			ratio of 4 (%)				ratio of 5 (%)				ratio of 6 (%)		
substrate	R	yield 4[a] (%)	*o*	*m*	*p*	yield 5[b] (%)	*o*	*m*	*p*	yield 6[b] (%)	*o*	*m*	*p*
1	OCH_3	85	75	–	25	5	55	–	45	2	50	–	50
2	*p*-OCH_3	65	–	–	100	6	–	–	100	0			
1	OH	75	60	–	40	0				0			
3	*o*-OH	53	100	–	–	0				0			
3	*p*-OH	47	–	–	100	0				0			
1	NH_2[c]	6	58	–	42	na[d]				na[d]			
2	*p*-NH_2[c]	4	–	–	100	na[d]				na[d]			
1	$NHCOCH_3$	67	67	–	33	na[d]				na[d]			
2	*p*-$NHCOCH_3$	60	–	–	100	na[d]				na[d]			
1	CH_3	14	62	8	30	23	34	41	25	2	30	40	30
3	*o*-, *m*-, *p*-CH_3[e]	57	19	4	77	26	14	43	43	0			
3	*m*-CH_3	19	–	100	–	62	–	100	–	0			
1	H	18				25				3			
2	H	58				28				2			
3	H	55				na[d]				na[d]			
1	Cl	10	49	2	49	21	22	66	12	3	25	50	25
2	*o*-, *m*-, *p*-Cl[f]	8	33	11	56	26	14	71	15	0			

[a] Yields are determined with the aid of ^{18}F as a tracer. [b] Yields are estimated from GCMS abundancies through comparison with those of solutions containing known mass amounts of the parent compounds. [c] The same results were obtained for *N*,*N*-dimethylaniline. [d] na = not analyzed by GCMS. [e] Mixture consisting of 18% *o*-, 6% *m*-, and 76% *p*-$CH_3C_6H_4HgCl$.[19] [f] Mixture consisting of 30% *o*-, 20% *m*-, and 50% *p*-ClC_6H_4HgOAc.

Table II. Effect of the Reaction Time on the Yield of the Fluorodemercuration Reaction of $CH_3C_6H_4HgCl$[a] Using (^{18}F)CH_3COOF

$C_6H_5OCH_3$ added after	^{18}F-toluenes (%)	^{18}F-anisoles (%)
1 min	38	33
2 min	44	19
5 min	53	5
10 min	56	0
60 min	56	0
10 min[b]	0	84

[a] *o*-, *m*-, and *p* mixture. [b] No $CH_3C_6H_4HgCl$ present.

was the main product. Interestingly, in the latter case the meta isomer of **5** predominated. This shift of reaction was also observed for the mercurated toluenes. From the mixture of isomers, relatively more of the meta isomer of **5** (R = CH_3) was formed as was confirmed by treatment of the pure meta-mercurated isomer. Apart from the methyl- and acetoxytoluenes, for **1**, R = CH_3 α-substitution was also observed leading to ethylbenzene and benzyl acetate. These latter two compounds were also obtained from dibenzylmercury in yields of 8% and 33%, respectively. By performing the reactions with gaseous acetyl hypofluorite and by using deuterioacetic acid as solvent, GCMS analysis revealed that the methyl and acetoxy group originated from acetyl hypofluorite and not from the solvent.

Apart from the observed substrate dependency, the fluorodemercuration is also dependent on the solvent used. In several solvents little or no fluorobenzene was obtained upon treatment of phenylmercury acetate. For anisole and its para-mercurated analogue the yields of the fluoroanisoles were—with the exception of tetrahydrofuran—comparable under the reaction conditions. By using, e.g., dichloromethane as solvent, GCMS analysis showed 1,1,2,2-tetrachloroethane to be the main product (15–20%) for **1–3** with R = CH_3, H, and Cl; for R = OCH_3 this product yielded about 5%. This means that in relatively slow reactions acetyl hypofluorite abstracts as a severe side reaction a hydrogen atom from the solvent molecules which again favors the use of acetic acid as solvent since its CH bond energy is one of the highest known.

Proposed Mechanism. Little is known of the chemical properties of acetyl hypofluorite in acetic acid solution. For the reaction of acetyl hypofluorite with activated aromatic compounds in freon, an addition–elimination mechanism in combination with a conventional electrophilic substitution has been proposed.[4,11] However, freon is a less polar solvent than acetic acid, whereas the formation of the methyl compounds **6** indicate that at least a part of the products are formed through a radical pathway. Interestingly, it has been shown that atomic fluorine detaches a hydrogen atom from benzene with the formation of phenyl radicals, while xenon difluoride reacts with benzene through a radical–cation mechanism.[12] The formation of aromatic radical–cations upon oxidation is commonly accepted.[13]

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Although a combination of several mechanisms can not be excluded, we feel that the one-electron oxidation as depicted in Scheme II is worthwhile to be considered for the reaction of aromatics with acetyl hypofluorite in acetic acid. This mechanism can account for all products formed. Initially, acetyl hypofluorite oxidizes the aromatic with the formation of a radical–cation, a fluoride anion, and an acetoxy radical. According to the Duwar–Zimmerman rules the approach of F^- to an aromatic radical–cation is an unfavorable process.[13b] However, for the anodic fluorination a complex between the electrode, the radical–cation, and the fluoride anion has been postulated as an intermediate, followed by a concerted process of a nucleophilic reaction and a second one-electron transfer.[13c] The role of the electrode can now be taken over by the acetoxy radical thus leading to the intermediate ii, which is identical with that of normal electrophilic reactions. The first oxidation step can, of course, only be carried out efficiently on electron-rich aromatics having a relatively low oxidation potential, while the polarity of the solvent must allow the creation of a ionic pair;[14] otherwise hydrogen abstraction might occur either from the solvent or from the aromatic. As to the second step, when intermediate ii is not really stabilized by electron-donating substituents, the fluoride anion has the alternative of acting like a base leading to a radical intermediate iii. Recombination of both radicals would give **5**, whereas a decomposition of the acetoxy radical during the process[15] can explain the formation of (nondeuterated) **6**.

For the mercury compounds (X = HgCl or HgOAc) the mechanism is almost identical. Since the mercury group is able to stabilize a positive charge, the charge in i is located mostly at the carbon atom attaching the mercury function, thus leading to a regiospecific fluorinated product **4**. Instead of proton abstraction the fluoride anion now has the alternative of performing a nucleophilic reaction on mercury, especially when mercury is attached to the less activated meta position, which accounts for the formation of the regiospecific (nondeuterio) acetoxylated product **5**.

Finally, this mechanism also explains why acetoxyphenol and methylphenol are not formed, and why in the case of toluene benzyl acetate and ethylbenzene are observed as byproducts. Obviously, proton abstraction in i should take place mainly at the phenolic function and partly also at the methyl group, respectively. For the anilines the one electron oxidation mainly occurs at the nitrogen lone pair resulting in very low yields of the corresponding fluoroanilines.

Experimental Section

For many of the experiments ^{18}F was used as a tracer, which permitted a simple determination of the yields of fluorinated products as radiochemical yields by using HPLC techniques.

$(^{18}F)F_2$ was prepared by the ^{20}Ne (d, α) ^{18}F reaction from ^{20}Ne containing 0.1% F_2 (35 μmol) in a monel target.[16] $(^{18}F)CH_3COOF$ was prepared by bubbling $(^{18}F)F_2$ through 15 mL of CH_3COOH[5] to which 180 μmol of $(NH_4)_2CO_3$ had been added. Gaseous $(^{18}F)CH_3COOF$ was produced by passing $(^{18}F)F_2$ through a column of KOAc/HOAc.[6] HPLC analysis of the (^{18}F)-fluoroproducts was performed on 20-cm C18 μ-Bondapack columns and on 50-cm silica columns. The following were eluents: CH_3OH/H_2O 50/50 (C18), n-C_6H_{14} (silica) for nitrobenzene, benzene, anisole, toluene, and chlorobenzene; CH_3OH/H_2O 30/70 (C18), EtOAc/n-C_6H_{14} 5/95 (silica) for phenol; CH_3OH/1 M NaOAc 20/80 (C18) for aniline, acetanilide, and N,N-dimethylaniline; CH_3OH/H_2O/HOAc 38/60/2 (C18) for benzoic acid.

Peaks were detected by a radioactivity monitor and a UV detector (254 nm); fractions of 500 μL were collected and counted. GCMS (type HP 5995A) analysis of the fluoro and byproducts was performed on a WCOT CP WAX 51 column (5 min 30 °C; after 5 min steps of 10 °C min^{-1} to 220 °C).

C_6H_5HgOAc, C_6H_5HgCl, p-$HOOCC_6H_4HgOAc$, p-$H_2NC_6H_4HgOAc$, and $(C_6H_5CH_2)_2Hg$ were purchased from Aldrich Europe; p-$CH_3CONHC_6H_4HgOAc$ was obtained by acylation of p-$NH_2C_6H_4HgOAc$ with acetic anhydride;[17] o- and p-HOC_6H_4HgCl were prepared as described by Dimroth;[18] nitrobenzene and toluene were mercurated by reaction of $Hg(ClO_4)_2$ according to Klapproth;[19] m-$CH_3C_6H_4HgCl$ was obtained from m-$CH_3C_6H_4MgBr$ and $HgCl_2$;[20] anisole,[21] chlorobenzene,[22] and N,N-dimethylaniline[17] were mercurated by reaction with $Hg(OAc)_2$.

Reaction of F_2 and CH_3COOF with the Mercury Compounds and Their Non-Mercurated Parent Compounds. $(^{18}F)F_2$ (30 μmol) was bubbled through 15 mL of CH_3COOH containing 150 μmol of substrate, or 3 mL of CH_3COOH containing 3–10 μmol of $(^{18}F)CH_3COOF$ was added to 30 μmol of substrate dissolved in 1 mL of CH_3COOH (for mechanistic studies other solvents were also used). In the case of deuterium experiments, 30 μmol of gaseous $(^{18}F)CH_3COOF$ was bubbled through 10 mL of CD_3COOD containing 150 μmol of substrate. After reaction (some 10 min), samples were withdrawn for HPLC analysis and yield determination. For the GCMS identification, the reaction mixture was diluted tenfold with water, after which, the products were absorbed on a Seppak-C18-cartridge column (Waters), eluted with 1.5 mL of CH_2Cl_2, and dried on $CaCl_2$. Identification of the fluoro compounds was performed by the comparison of the HPLC retention times with those of authentic samples and by GCMS analysis. The methyl and acetoxy compounds were identified by comparing the GC retention times and mass spectra with those of authentic samples or by comparison of the mass spectra with those reported in the literature.[23]

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Registry No. **1** (R = OMe), 100-66-3; **1** (R = OH), 108-95-2; **1** (R = NH_2), 62-53-3; **1** (R = $NHCOCH_3$), 103-84-4; **1** (R = CH_3), 108-88-3; **1** (R = H), 71-43-2; **1** (R = Cl), 108-90-7; **2** (R = p-OMe, 5780-90-5; **2** (R = p-NH_2), 6283-24-5; **2** (R = p-$NHCOCH_3$), 7299-21-0; **2** (R = H), 62-38-4; **2** (R = o-Cl), 71205-14-6; **I** (R = m-Cl), 71205-15-7; **I** (R = p-Cl), 21843-82-3; **3** (R = o-OH), 90-03-9; **3** (R = p-OH), 623-07-4; **3** (R = o-CH_3), 2777-37-9; **3** (R = m-CH_3), 5955-19-1; **3** (R = p-CH_3), 539-43-5; **3** (R = H), 100-56-1; **4** (R = o-OMe), 321-28-8; **4** (R = p-OMe), 459-60-9; **4** (R = o-OH), 367-12-4; **4** (R = p-OH), 371-41-5; **4** (R = o-NH_2), 348-54-9; **4** (R = p-NH_2), 371-40-4; **4** (R = o-$NHCOCH_3$), 399-31-5; **4** (R = p-$NHCOCH_3$), 351-83-7; **4** (R = o-Me), 95-52-3; **4** (R = p-Me),

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352-32-9; **4** (R = *m*-Me), 352-70-5; **4** (R = H), 462-06-6; **4** (R = *o*-Cl), 348-51-6; **4** (R = *p*-Cl), 352-33-0; **4** (R = *m*-Cl), 625-98-9; **5** (R = *o*-OMe), 613-70-7; **5** (R = *p*-OMe), 1200-06-2; **5** (R = *o*-Me), 533-18-6; **5** (R = *m*-Me), 122-46-3; **5** (R = *p*-Me), 140-39-6; **5** (R = *o*-Cl), 4525-75-1; **5** (R = *m*-Cl), 13031-39-5; **5** (R = *p*-Cl), 876-27-7; **5** (R = H), 122-79-2; F_2, 7782-41-4; CH_3COOF, 78948-09-1; *N,N*-dimethylaniline, 121-69-7.

The Stereochemistry of 2,6-Di-*tert*-butyl-1,2,5,6-tetrahydropyridine and *cis*- and *trans*-2,6-Di-*tert*-butylpiperidine

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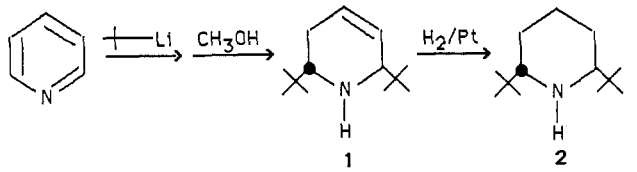
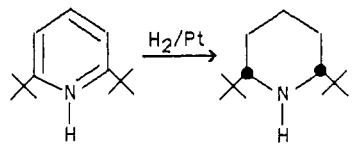
The isolation of 2,6-di-*tert*-butyl-1,2,5,6-tetrahydropyridine (**1**) from a reaction of pyridine with excess *tert*-butyllithium has been reported from this laboratory.[1] Catalytic hydrogenation of tetrahydropyridine **1** gave a product whose spectral and elemental analyses were in agreement with a 2,6-di-*tert*-butylpiperidine (**2**). Piperidine **2** was assumed to be the trans isomer based on the following observations.



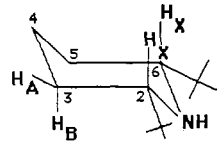
1 **2**



3 **4**

Catalytic hydrogenation of 2,6-di-*tert*-butylpyridine (**3**) produced a 2,6-di-*tert*-butylpiperidine (**4**) whose spectral properties were different from those of piperidine **2**. Because of the preference for syn addition of hydrogen in catalytic hydrogenation, piperidine **4** was assumed to be *cis*-2,6-di-*tert*-butylpiperidine. In addition, the ^1H and ^{13}C NMR data for piperidine **4** were in agreement with those reported by Day[2] for *cis*-2,6-di-*tert*-butylpiperidine obtained from the reduction of 2,6-di-*tert*-butylpyridine with lithium in 1,2-ethanediamine.

The assignment of a cis configuration to piperidine **4** is also supported by partial analysis of its NMR spectrum. In *cis*-2,6-di-*tert*-butylpiperidine (**4**), the trans coupling between protons H_B and H_X is expected to be much larger than the gauche coupling between protons H_A and H_X. Booth and Little[4] have shown these values to be 10.6 and 1.9 Hz, respectively, for *cis*-2,6-dimethylpiperidine. By first-order analysis of the doublet of doublets at 2.12 ppm, the trans and gauche coupling constants $J_{B,X}$ and $J_{A,X}$ in piperidine **4** were determined to be 10.2 and 1.8 Hz, respectively. These data support a conformationally rigid structure for *cis*-2,6-di-*tert*-butylpiperidine (**4**) in which the protons at C_2 and C_6 (H_X) occupy axial positions.



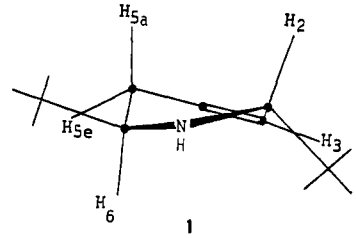
4

Allinger[3] has shown by thermodynamic studies that *trans*-1,3-di-*tert*-butylcyclohexane exists in a twist-boat conformation, and piperidine **2** was expected to exhibit the same stereochemistry. This paper deals with NMR studies which confirm these initial stereochemical assignments.

The ^1H NMR spectrum of the compound assumed to be *trans*-2,6-di-*tert*-butylpiperidine (**2**) shows a singlet at 0.90 ppm for the *tert*-butyl groups and a doublet of doublets at 2.40 ppm assigned to the protons at C_2 and C_6. The remainder of the spectrum is a complex of absorption lines between 1.09 and 1.51 ppm. Analysis of the stereochemistry of piperidine **2** by NMR shift reagent studies was unsuccessful. Generally, the shift reagents produced only small chemical shifts associated with signal broadening. However, 2,6-di-*tert*-butyl-1,2,5,6-tetrahydropyridine (**1**), the precursor of piperidine **2** did produce distinct lanthanide-induced chemical shifts with Yb(FOD)$_3$ and was chosen for study. Since the synthesis of piperidine **2** from tetrahydropyridine **1** only requires catalytic reduction of the carbon–carbon double bond, we assumed that the configuration of the *tert*-butyl groups would remain unchanged in the conversion of **1** to **2**.

The ^1H NMR studies of the stereochemistry of tetrahydropyridine **1** focused on a twist-boat conformation in which the *tert*-butyl groups occupy pseudoequatorial positions. A cis configuration was ruled out because of the previously mentioned comparison of the reduction products of tetrahydropyridine **1** and of 2,6-di-*tert*-butylpyridine. A chair conformation of the trans isomer seemed unlikely since, in this conformation, a *tert*-butyl group would be required to occupy an axial position. These conclusions are supported by the data obtained from chemical shift reagent studies which are incompatible with either the cis configuration of a chair conformation of the trans isomer.

The ^1H NMR spectrum of tetrahydropyridine **1** shows two singlets at 0.93 and 0.97 ppm (*tert*-butyl groups), a singlet at 1.33 ppm (NH), a complex multiplet centered at 1.90 ppm (H_5, H_6), a doublet of doublets at 2.64 ppm (H_7), a multiplet centered at 3.04 ppm (H_2), and a complex multiplet at 5.87 ppm (H_3, H_4). The chemical shift assignments in tetrahydropyridine **1** are in general agreement with those assigned by Shoolery[6] to the protons in 1,2,5,6-tetrahydropyridine.



1

The lanthanide-induced chemical shifts, summarized in Figure 1, show that H_2 and H_{5a} experience large chemical shifts and that each is shifted approximately the same. This result suggests that these protons are in close proximity to the lanthanide metal location. A trans relation-

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