optical density at the appropriate wavelengths, usually 315 and 295 nm. The rate constants were determined from the slope of a plot of log A/A_o vs. time by using the infinity optical density for the value of A_o. The plots showed excellent linearity up to three to four half-lives. Representative data are given in the supplementary material. The rate constants were readily reproducible within ±5% and should be accurate within ±10%.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and to the National Science Foundation for partial support of this research.

Supplementary Material Available: Experimental details of the structure proofs for compounds **13b,c,e-k** and **14b,c,e-h** and representative kinetic plots of the data (14 pages). Ordering information is given on any current masthead page.

Fluorination of Aromatic Derivatives with Fluoroxytrifluoromethane and Bis(fluoroxy)difluoromethane

Michael J. Fifolt,* Raymond T. Olczak, and Rudolph F. Mundhenke

Occidental Chemical Corporation, Grand Island Research Center, Grand Island, New York 14072

Joseph F. Bieron

Department of Chemistry, Canisius College, Buffalo, New York 14208

Received August 16, 1984

Fluoroxytrifluoromethane (CF_3OF) and bis(fluoroxy)difluoromethane $CF_2(OF)_2$ are formed by the reaction of F_2 with CO and CO_2, respectively, over a CsF catalyst in a continuous-stream process. Both reagents react with aromatic substrates by an electrophilic substitution mechanism to yield fluoro-substituted derivatives. Fluorobenzene is produced in good yield from benzene, and aniline derivatives afford monofluorination products. Acetanilide (**1**), *N*-phenylmethanesulfonamide (**2**), α,α,α-trifluoroacetanilide (**3**), and 1,1,1-trifluoro(*N*-phenyl)methanesulfonamide (**4**) react with either reagent to yield mixtures of *o*- and *p*-fluoro-substituted derivatives. Solvent effects and competitive rate experiments demonstrate a preference for ortho substitution, especially in aprotic, nonpolar solvents. With particular substrates, these fluorinating agents are of practical synthetic utility, e.g., 2-fluoro-4-(trifluoromethyl)aniline is produced in high yield by fluorinating the intermediate 4-(trifluoromethyl)acetanilide (**6**) with CF_3OF. Activated substrates such as toluene, xylenes, anisole, and cresols give mixtures of products which reduce the synthetic utility of these reagents. Nitrobenzene is fairly unreactive toward CF_3OF and gives low yields of substitution products.

The selective introduction of fluorine on an aromatic ring is not an easy synthetic task, and interest remains high in this type of process because fluoro-substituted aromatic derivatives show promise in a variety of applications, from agricultural chemicals to pharmaceuticals.

The Schiemann reaction, in which a diazonium, tetrafluoroborate is decomposed, converts an aniline to a fluorobenzene derivative, is the prominent method.[1] However, the reaction conditions, variable yields, and troublesome byproducts make this reaction a poor selection for any large scale industrial process.

Chloro- or bromo-substituted aromatic compounds bearing electron-withdrawing groups react under vigorous conditions with fluoride ion by nucleophilic displacement to yield fluoro derivatives. The positional requirement for electron-withdrawing substitutents limits the synthetic utility of this type of reaction.

Chlorination and bromination by a variety of reagents are usually accomplished by electrophilic substitution reactions. However, there are few fluorinating agents that introduce fluorine on an aromatic ring under selective and controlled conditions. Reactions with elemental fluorine afford unselective polyfluorination of the ring because of fluorine's extreme reactivity. The reactivity of fluorine can be quantitatively related to other halogens.[2] Reactions conducted at high dilution and extremely low conversion levels yield a Hammett-type correlation where $\rho^+ = -2.45$ when δ^+ values were used. This compares to typical values for chlorination ($\rho^+ = -6$ to -9) and bromination ($\rho^+ = -13$) which show fluorination to have a very low activation energy in electrophilic aromatic substitution reactions. Although isolated reports have appeared which claim selective fluorination with F_2,[3] there is, as yet, no optimum synthetic method.

In the design of an acceptable fluorinating agent, the strategy has been adopted of first treating elemental fluorine with another reagent to make it less reactive in subsequent reactions. There are a number of examples in this category. Xenon difluoride, XeF_2, does fluorinate both activated and deactivated substituted aromatic rings in moderate and varying yields.[4] Elemental fluorine reacts with sodium acetate to yield acetyl hypofluorite, CH_3CO-OF, which exhibits reactions that lead to monofluorination of activated aromatic rings.[5] Cesium fluoroxysulfate[6] and silver difluoride[7] have also been demonstrated to be reagents that yield selective monofluorination of aromatic substrates.

(1) For a general review of fluorinated aromatic compounds see: Boudakian, M. M. *Kirk-Othmer Encycl. Chem. Technol., 3rd ed.* **1980**, *10*, 901-36.

(2) (a) Cacase, F.; Wolf, A. P. *J. Am. Chem. Soc.* **1978**, *100*, 3639. (b) Cacase, F.; Giacomello, P.; Wolf, A. P. *J. Am. Chem. Soc.* **1980**, *102*, 3511.

(3) Misaki, S. *J. Fluorine Chem.* **1981**, *17*, 159.

(4) (a) Anand, S. P.; Quarterman, L. A.; Hyman, H. H.; Migliorese, K. G.; Filler, R. *J. Org. Chem.* **1975**, *40*, 807. (b) Anand, S. P.; Quarterman, L. A.; Christian, P. A.; Hyman, H. H.; Filler, R. *J. Org. Chem.* **1975**, *40*, 3796. (c) Filler, R. *Isr. J. Chem.* **1978**, *17*, 71.

(5) Lerman, O.; Tor, Y.; Rozen, S. *J. Org. Chem.* **1981**, *46*, 4629.

(6) Stavher, S.; Zupan, M. *J. Chem. Soc., Chem. Commun.* **1981**, 148.

(7) Zweig, A.; Fischer, R. G.; Lancaster, J. E. *J. Org. Chem.* **1980**, *45*, 3597.

0022-3263/85/1950-4576$01.50/0

Fluoroxytrifluoromethane (FTM), CF_3OF, one of the fluorinating agents discussed in this work, has been used previously and it reacts with a variety of functional groups.[8] FTM reacts with saturated hydrocarbons by substituting fluorine for hydrogen.[9] and adds to a double bond to yield an adduct containing –F and $–OCF_3$ on vicinal carbons.[10] Reactions of FTM with amines and amides give *N*-fluoro derivatives with varying degrees of stability under the reaction conditions.[11] In the reaction of FTM with double bonds, there is evidence to support both free radical and electrophilic addition mechanisms, which suggests that the operative mechanism is determined by the reaction conditions.

FTM also reacts readily with aromatic substrates to yield fluoro-substituted products. The postulated mechanism involves electrophilic aromatic substitution with the O–F bond polarized to yield fluorine with a partial positive charge as it undergoes reaction.[8c] This view has been criticized and the mechanism of aromatic substitution has not been substantially addressed at this time.[12]

This work will describe the behavior of two fluorinating reagents, fluoroxytrifluoromethane (FTM) and bis(fluoroxy)difluoromethane (BDM), with a variety of aromatic substrates. We have investigated the mode of addition, product distribution, solvent effects, and relative rates of reaction which allow us to comment on the reaction in some detail.

FTM is prepared by the reaction of elemental fluorine with carbon monoxide. The initial product is carbonyl fluoride formed by a spontaneous and highly exothermic reaction. This product is passed through a bed of cesium fluoride which catalyzes addition of a second mole of fluorine.

$$C{\equiv}O + F_2 \rightarrow \begin{matrix} F \\ \diagdown \\ C{=}O \\ \diagup \\ F \end{matrix} \xrightarrow[F_2]{CsF} CF_3OF$$

BDM is produced in a similar manner by reaction of carbon dioxide with fluorine. In this case, preparation of the cesium fluoride catalyst by fusion and subsequent grinding under anhydrous conditions is critical for the reaction to occur.[13]

$$O{=}C{=}O \xrightarrow[F_2]{CsF} CF_2\begin{matrix} \diagup OF \\ \diagdown OF \end{matrix}$$

Both FTM and BDM can be prepared in greater than 95% purity and have been stored under pressure in lecture bottles for approximately 2 years with very little decomposition, indicating that they are both fairly stable compounds. The safe handling of these gases does not require any special precautions after the conditions for the safe handling of fluorine gas have been met. The use of fluorine does require special handling, which is well documented, and one should not attempt either of the reactions without careful attention to handling these toxic and highly corrosive materials. Consult the Experimental Section for details on the safe handling of these reactants. Table I lists some of the physical properties of FTM and BDM.

Table I. Some Physical and Chemical Properties of (Fluoroxy)trifluoromethane (FTM) and Bis(fluoroxy)difluoromethane (BDM)

property	FTM	BDM
formula	CF_3OF	$CF_2(OF)_2$
mp, °C	below −215[a]	below −196 (glass)[b]
bp, °C	−97[a]	−64[b]
vapor pressure	log P(cm) = 6.0059 − 656.22/T − 13988/T^2[a]	log P (mm) = 7.530 − 971.6/T[b]
density, g/cm^3	1.9 (at −95 °C)[a]	1.62 (at −64 °C)[b]
ΔH_{vap}, cal/mol	3710[a]	4445[b]
ΔH_{form}, kcal/mol	−184.0 ± 2.5[c]	−130.5 ± 3.0[c]
^{19}F NMR ($CFCl_3$ ref)	CF_3OF −147.1 CF_3OF +72.3	$CF_2(OF)_2$ −159.2[b] $CF_2(OF)_2$ +84.2 J_{F-F} = 39 Hz
thermal stability	stable in copper[a] tube 450 °C	150 °C, 6 h, 100% unchanged[b] 200 °C, 14 h, 80% unchanged
	reversible dissociation[d] at 375 °C	250 °C, 3 h, 40% unchanged 275 °C, 13 h, 3% unchanged 300 °C, 3.5 h, 12% unchanged

[a] Kellogg, K. B.; Cady, G. H. *J. Am. Chem. Soc.* **1948**, *70*, 3986. [b] Thompson, P. G. *J. Am. Chem. Soc.* **1967**, *89*, 1811. [c] Foss, G. D.; Pitt, D. A. *J. Phys. Chem.* **1968**, *72*, 3512. [d] *Inorg. Synth.* **1966**, *8*, 165.

Reactions of CF_3OF and $CF_2(OF)_2$ with Aromatic Substrates

Both CF_3OF (FTM) and $CF_2(OF)_2$ (BDM) react with a variety of aromatic substrates in a manner characteristic of electrophilic species. The nature of the substituent already present plays a major role in determining the ease and extent of fluorine substitution.

Reactions with Benzene. Benzene reacts readily with FTM and BDM to give fluorobenzene in varying yields, depending on reaction conditions and conversion rates. The maximum yield of fluorobenzene is obtained around 40% conversion. The yield is 93% based on a conversion rate of 41% along with 5% of (trifluoromethoxy)benzene, based on the same conversion rate. Further fluorination results in the products competing for FTM or BDM and yielding multi-substituted products. Addition of K_2CO_3 to react with liberated HF shows little effect, and the reaction can be run without solvent at low conversion. These experiments demonstrate that FTM is an excellent fluorinating agent for the synthesis of fluorobenzene if the reaction is carried out at low conversion levels. However, since benzene and fluorobenzene have very similar boiling points, the difficulty of separating and recycling benzene remains a major problem in any large scale synthesis.

In terms of mechanism, the hypothesis is made that the reaction proceeds through an electrophilic substitution reaction to yield the principal product fluorobenzene. (Trifluoromethoxy)benzene probably results from addition of CF_3OF to benzene with subsequent elimination of HF. Subsequent reactions will be presented that support this hypothesis.

Activated Aromatics. Alkyl substituents, using toluene and *o*-xylene as examples, have been investigated. The reactions provide a variety of products and poor material balance. Even at low conversion rates, the yield of monofluoro substitution products from toluene is low. In the case of *o*-xylene, in addition to ring fluorination, product analysis indicates OCF_3-containing products by GC–MS

(8) (a) Kellogg, K. B.; Cady, G. H. *J. Am. Chem. Soc.* **1948**, *70*, 3986. (b) Kollonitsch, J.; Barash, L.; Doldouras, G. A. *J. Am. Chem. Soc.* **1970**, *92*, 7494. Kollonitsch, J. U.S. Patent 4030944, June 21, 1977, For reviews, see: (c) Lustig, M.; Shreeve, J. M. "Adv. Fluorine Chem."; CRC Press: Cleveland, Ohio, 1973; Vol 7, pp 175–198. (d) Hesse, R. H. *Isr. J. Chem.* **1978**, *17*, 60.

(9) Barton, D. H. R.; Hesse, R. H.; Mackwell, R. E.; Pechet, M. H. *J. Am. Chem. Soc.* **1976**, *98*, 3034.

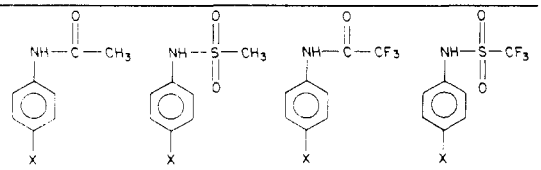
(10) Barton, D. H. R.; Hesse, R. H.; Jackman, G. P.; Ogunkoya, L.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1*, **1974**, 739.

(11) Barton, D. H. R.; Hesse, R. H.; Pechet, M. M.; Toh, H. T. *J. Chem. Soc., Perkin Trans 1*, **1974**, 732.

(12) Christe, K. O. *J. Fluorine Chem.* **1983**, *22*, 519.

(13) Fifolt, M. J. U.S. Patent 4499024, 1985.

Table II. NMR Chemical Shifts for N-Substituted Aniline Derivatives



	1	2	3	4
[a]para ^{13}C (X = F)	123.4	124.6	126.6	127.2
[a]para ^{19}F (X = F)	−120.3	−118.9	−116.8	−115.4

[a] Chemical shifts are reported in ppm shifts; ^{13}C with Me_4Si, ^{19}F from $CFCl_3$.

which are not completely characterized. It is clear that addition of FTM to alkyl substituted aromatic substrates is not yet a useful synthetic method. Besides electrophilic substitution of fluorine, side chain fluorination and addition to the ring are competing reactions.

We have investigated the reaction of FTM with anisole, *m*-cresol, and *p*-cresol. A number of experiments were run with anisole. At low temperature and less than the stoichiometric amount of FTM added, the yield of monofluoro anisoles is fairly good (at a conversion rate of 82%, yield of *o*- + *p*-fluoroanisole is 67%). As the temperature is lowered, the amount of monofluoro derivatives remain fairly constant but the ortho/para ratio changes. In a polar, hydrogen-bonded solvent, the para isomer is slightly favored. In this case, with the methoxy group as a substituent, the ring is activated sufficiently to favor electrophilic substitution over competing reactions, as was shown in the previous examples of toluene and *o*-xylene.

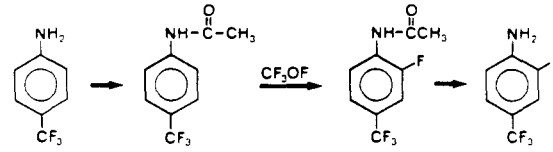
The reaction with *m*- and *p*-cresol lead to a number of products which were not completely characterized. Reaction of *m*-cresol in trifluoroacetic acid at 0 °C, produced unreacted *m*-cresol (18%), 6-fluoro-3-methylphenol (18%), and an unresolved mixture of 4-fluoro- and 2,6-difluoro-3-methylphenols (58%) with analysis done by ^{13}C NMR. The reaction of *p*-cresol with FTM gave a mixture of monofluorinated cresols plus 4-fluoro-4-methylcyclohexadienone in a 3/2 ratio as analyzed by GC/MS. Similar addition of fluorine to phenols instead of substitution has been previously reported.[3] Sufficient experiments were done to indicate that reaction of phenols with FTM is not a good synthetic reaction route.

Deactivated Aromatics. BDM and FTM do not readily react with aromatic substrates which bear electron-withdrawing substituents. Nitrobenzene is unreactive toward electrophilic substitution by either FTM or BDM. Dilute elemental fluorine (1/10 mixture in nitrogen) yields similar results by comparison. Although the products were not isolated and characterized, spectral evidence indicates that most of the unrecovered product results from addition to the aromatic ring. Other electron-withdrawing substituents showed similar results. Other substrates reacted with benzotrifluoride, benzonitrile, benzoic acid, and phthalic anhydride. The experiments were initially attempted because the potential one-step synthetic route to meta-substituted fluorobenzenes is very attractive, but poor yields in exploratory experiments discouraged further efforts.

Fluorination with FTM in a Synthetic Method

We cite an example at this point of the use of FTM as a fluorinating agent in a reaction sequence where it is the reagent of choice.

A valuable intermediate in agricultural chemistry is 2-fluoro-4-(trifluoromethyl)aniline. This compound was synthesized in good yield on a 20-g scale in the following manner. (Overall yield for the reaction sequence was 57%.)



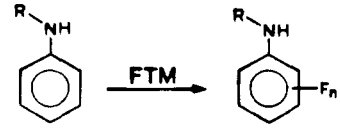
The reaction sequence is fairly general and fluorination occurs in a similar manner if the trifluoromethyl group is replaced by other electron-withdrawing substituents such as chloro, nitro, or cyano groups. Apparently, the combination of two substituents, one activating and the other deactivating, and substituted para to one another, is favorable for good yields of the monofluorination products.

Reactions of FTM and BDM with N-Substituted Aniline Derivatives

As shown above, N-substituted aniline derivatives react cleanly with FTM and BDM to give high yields of ortho and para monosubstituted fluoro derivatives. The four compounds that were studied extensively are acetanilide (**1**), *N*-phenylmethanesulfonamide (**2**), α,α,α-trifluoroacetanilide (**3**), and *N*-phenyl-1,1,1-(trifluoromethane)-sulfonamide (**4**). (Structures are shown in Table II.)

These substrates were found to be suitable for investigating the mechanism of fluorination with FTM and BDM. The reaction can be carried out in a variety of solvents. Table III gives a brief summary of the product distribution for the four derivatives. Initial screening experiments

Table III. Summary of Product Distribution for N-Substituted Aniline Derivatives



			product distribution, %						
R group	solvent	excess reagent	unreacted	*o*-F	*p*-F	2,4-di-F	2,6-di-F	material recovery	ortho/para
$COCH_3$	$CHCl_3$	FTM	10	37	17	10	3	77	2.2
$COCH_3$	$CHCl_3$	FTM	4	44	11	3	8	70	4.0
SO_2CH_3	$CHCl_3$	FTM	–	44	7	11	4	66	6.3
$COCH_3$	CF_3CO_2H	FTM	10	37	17	10	3	77	2.2
$COCF_3$	CF_3CO_2H	FTM	1	44	18	7	2	72	2.4
SO_2CH_3	CF_3CO_2H	FTM	12	60	18	4	4	95	3.3
SO_2CH_3	CF_3CO_2H	BDM	3	38	12	10	1	64	3.2
SO_2CF_3	CF_3CO_2H	FTM	6	44	38	6	–	94	1.2
SO_2CF_3	CF_3CO_2H	BDM	5	39	29	2	–	75	1.3

Table IV. Fluorination of N-Substituted Anilines with FTM and BDM Influence of Solvent on Ortho/Para Ratio

solvent category	substrate			
	CH_3CO-	CF_3CO-	CH_3SO_2-	CF_3SO_2-
aprotic, nonpolar: $CHCl_3$, CCl_4	2.2–2.8[a] (2.4–5.0)[b]	2.9–6.7 (3.4–6.4)	3.7–8.8 (3.3–6.0)	2.0–3.5
aprotic, polar: CH_2Cl_2, $(CH_3)_2CO$, CH_3NO_2, CH_3CN	1.7–2.0 (1.5–3.6)	1.5–2.4 (1.8–2.8)	1.6–2.6 (1.5–2.3)	1.0–1.3
protic, polar: CH_3OH, $(CH_3)_3COH$, HCO_2H, CH_3CO_2H, CF_3CO_2H	1.5–2.0 (2.0–2.6)	1.0–2.0 (1.0–2.0)	2.6–3.7 (2.2–3.0)	0.7–1.5

[a] For each entry, a range of values is given which includes all experimental data for the indicated group of solvents. [b] Values for reactions with BTM are given in parentheses.

indicated that the product distribution was dependent on a number of variables: the nature of the substituent, solvent, percent conversion, and to a much lesser degree, temperature. To investigate these more closely, a number of sets of experiments were conducted. Each of the four substrates were fluorinated in approximately 12 different solvents. Since secondary reactions occur, the ortho/para ratio was determined at low conversion rates, between 10 and 20% conversion of starting materials to products. In each set, the temperature, in one solvent, was varied over a range of 75 to 100 °C. The percent conversion was also systematically varied in one solvent. To complete the set of experiments, fluorination with FTM was compared to that with BTM.

A number of observations can be made about the data and summarized as follows:

(1) A change in temperature over a range of approximately 100 °C has very little effect on the product distribution of the reaction. The reaction occurs very fast and the experiments were not designed to observe changes in the rates of reaction. The course of the reaction cannot be varied by a change in temperature under our experimental conditions.

(2) The product distribution does not change greatly if the conversion rate is kept below 50–60%. Addition of more fluorinating agent not only results in multi-fluoro substitution but also in unidentified products that decrease the recovery of material.

(3) The product distribution is affected by the solvent, and it is not the same for all substrates. The ortho/para ratio varies with both a change of substituent and with the type of solvent. If reactivity at the ortho and para positions were equal, the ratio would equal two on a statistical basis. Ortho substitution is highly favored in the nonpolar solvent CCl_4, while in polar solvents the ratio is usually less than two. Protic solvents appear to favor the para position. The data are not precise enough to warrant any attempt at quantitative relationships between solvent parameters and ortho–para ratios but qualitative groupings have been made, as summarized in Table IV.

Based on these differences in product distribution as a function of amide type and solvent, we were prompted to investigate relative reactivities of the compounds under investigation. These experiments are discussed next.

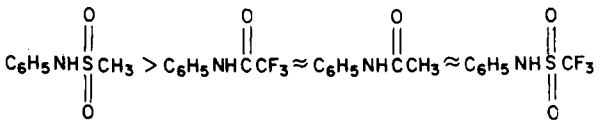
Relative Reactivities of N-Substituted Aniline Derivatives

It is of interest to compare the relative reactivity of the four N-substituted aniline derivatives: acetanilide (1), *N*-phenylmethanesulfonamide (2), α,α,α-trifluoroacetanilide (3), and *N*-phenyl-1,1,1-trifluoromethanesulfonamide (4). These compounds are listed in Table II along with carbon-13 and fluorine-19 NMR chemical shifts for carbon and fluorine at the para position.

The chemical shifts for both ^{13}C and ^{19}F have been correlated in Hammett-type relationships, and it has been demonstrated with a variety of functional groups that reactivity can be predicted on the basis of this type of data.[14] It is predicted that acetanilide 1 should be most reactive, and reactivity decreases from substrate 1 through 4, assuming that reaction with FTM has a negative ρ value.

The relative reactivities of these derivatives can best be determined by conducting competitive rate experiments between pairs of compounds. Reactions were run with a deficiency of CF_3OF, and product distribution was analyzed by capillary-column gas chromatography. All the fluorinated substrates were synthesized independently, which allowed for quantitative analysis using internal standards. All competitive experiments were conducted at least twice.

From these data an order of reactivity has been determined which is different than that predicted above. The relative reactivities are as follows:



The experiments show that *N*-phenylmethanesulfonamide is the most reactive toward fluorination and the other three derivatives are of comparable reactivity and do not exhibit an order which is predicted by straightforward electronic interactions of the substituent with the reaction center. The data yield two additional pieces of information. The ortho/para ratio is significantly higher for the more reactive sulfonamide 2 and secondly, the very small amount of the disubstituted derivative formed in each instance is the 2,6-difluoro and not the 2,4-derivative. Both observations give indication that there is a preference for the ortho position in the case of the more reactive compound.

To further demonstrate increased reactivity at the ortho position, competitive rate experiments were conducted between acetanilide and the ortho- and para-disubstituted trifluoromethyl derivatives 5 and 6. As anticipated, the trifluoromethyl group deactivates the aromatic ring and makes 5 and 6 less reactive than acetanilide. Of significance is the observation that *p*-(trifluoromethyl)acetanilide (6) is at least five times more reactive than *o*-(trifluoromethyl)acetanilide (5).

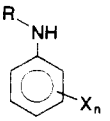
Lastly, an experiment which bears on the mechanism was a competitive rate experiment between acetanilide and *N*-methylacetanilide with deficiency of FTM. There was no detectable fluorination product of *N*-methylacetanilide after 57% reaction of acetanilide and consumption of all the available FTM. The presence of an amido hydrogen greatly enhances the rate of reaction.

Discussion of Results

In discussing the mechanistic inferences of our experimental observations, we will use fluoroxytrifluoromethane (FTM) as the prime example of the fluorinating agent. Previous discussions in the literature[8c] give evidence and

(14) Ehrenson, S.; Brownlee, J. C.; Taft, R. W. *Prog. Phys. Org. Chem.* **1973**, *10*, 1, and references therein.

Table V. Physical Properties of N-Substituted Aniline Derivatives[a]



R	X	mp, °C	lit. mp, °C
$-COCH_3$	H	113–115	115–6[b]
$-COCH_3$	2-F	78–79	75.6–76.1[c]
$-COCH_3$	4-F	151–153	152[b]
$-COCH_3$	2,4-F	121–123	
$-COCH_3$	2.6-F	146–147	144.5–145[d]
$-COCF_3$	H	86–88	88.5–90[e]
$-COCF_3$	2-F	68–69	
$-COCF_3$	4-F	111–112.5	112[f]
$-COCF_3$	2.4-F	54–55.7	
$-COCF_3$	2,6-F	76.5–78	
$-SO_2CH_3$	H	97.5–100.5	99–100[g]
$-SO_2CH_3$	2-F	74.8–75.8	
$-SO_2CH_3$	4-F	104–105	105.5[f]
$-SO_2CH_3$	2,4-F	96–98.8	
$-SO_2CH_3$	2,6-F	141.5–143	
$-SO_2CF_3$	H	66–67.7	65–66[h]
$-SO_2CF_3$	2-F	67–69	65.5–67.5[i]
$-SO_2CF_3$	4-F	61–63	60.5–62.5[f]
$-SO_2CF_3$	2,4-F	66–67	64–65.5[i]
$-SO_2CF_3$	2,6-F	93–94	

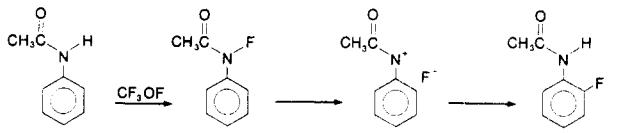
[a] Satisfactory analytical data (±0.4% for C, H, N, F) were reported for all compounds where a literature melting point is not listed. [b] "Dictionary of Organic Compounds", 5th ed.; Chapman and Hall: New York, 1982; entry A-02999. [c] Jart, A.; Lundt, I. *Acta Chem. Scand.* **1966**, *19*, 2404. [d] Hodgon, H.; Nicholson, D. *J. Chem. Soc.* **1960**, 5259. [e] Ishikawa, N.; Namkung, J. J.; Fletcher, T. L. *J. Org. Chem.* **1965**, *30*, 3878. [f] Bourne, E. J.; Henry, S. J.; Tatlou, C. E. M.; Tetlow, J. C. *J. Chem. Soc.* **1952**, 4014. [g] Dronkina, M. I.; Syrova, G. P.; Grandel'sman, L. Z.; Sheinker, Y. N.; Yagupol'skii, L. M. *J. Org. Chem. USSR (Engl. Transl.)* **1972** *8*, 7. [h] Backer, H. J. *Recl. Trav. Chim. Pays-Bas* **1951**, *70*, 92. [i] Brice, T. J.; Trott, P. W. U.S. Patent 2732398, 1956. [j] Trepka, R. D.; Harrington, J. K.; McConville, J. W.; McGurran, K. T.; Mendel, A.; Pauly, D. R.; Robertson, J. E.; Waddington, J. T. *J. Agric. Food Chem.* **1974**, *22*, 1111.

explanations that show FTM to undergo polarization in its reactions that places a partial positive charge on the fluorine, making it an electrophilic reagent. Recently, another plausible explanation has been postulated.[15] FTM can be viewed as a molecule which is not highly polarized. During reaction, if the fluorine has an affinity for election density in a reacting substrate, the reaction will be facilitated because the trifluoromethoxy ion becomes an excellent leaving group. If bond breaking and bond making are concerted, no development of positive charge on the fluorine need be postulated.

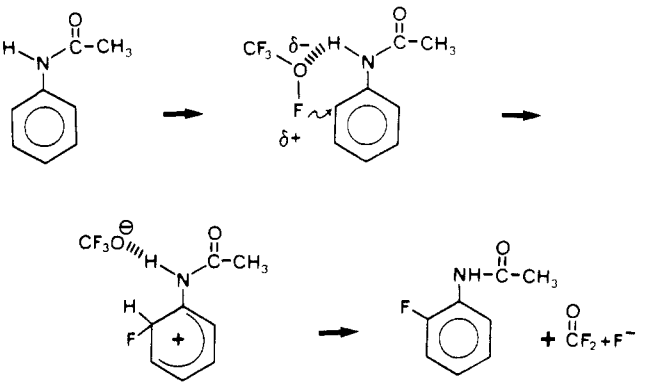
The premise is made that reaction of FTM with aromatic substrates proceeds by way of an electrophilic substitution mechanism. Supporting data include qualitative correlation among reactivity of substituent groups as well as orientation effects that are consistent with an electrophilic aromatic substitution mechanism. In the N-substituted aniline series, there was no evidence of the meta-fluoro isomer in the product distribution. The ortho–para-directing influence of these moderately activating groups was clearly evident. It is only in the case of highly activated substrates, like *p*-cresol, that an addition reaction may compete with the much more prevalent substitution reaction. Trifluoroacetic acid appears to be an excellent solvent for this reaction. FTM is soluble in TFA but does not react to any extent with it. TFA exhibits hydrogen bonding with FTM and facilitates polarization so that reactivity is enhanced.

Specifically with respect to the substituted anilide substrates, the relative reactivity difference between *o*- and *p*-(trifluoromethyl)acetanilides clearly demonstrate a preference for the ortho position. This selectivity is promoted by reaction in the nonpolar solvent CCl_4. These observations support the hypothesis that FTM reacts with the amide hydrogen in nitrogen derivatives before it attacks the ring. This is supported by the low reactivity of N,N-disubstituted anilines. *N*-methylacetanilide is a compound that demonstrates this low reactivity.

In reviewing the data, there are two plausible mechanistic explanations for increased reactivity at the ortho position. There is precedence in the literature for a nitrenium intermediate if analogy is made to the mechanism for chlorination of substituted anilines.[16] N-Fluorination could occur with subsequent heterolytic bond cleavage to an ion pair involving a nitrenium ion and fluoride ion.



In nonpolar solvents, the tight ion pair would favor ortho substitution in accord with our observation. An alternative postulate would involve hydrogen bonding between the amido hydrogen and FTM which would polarize the reagent and facilitate generation of electrophilic fluorine.



Our experimental data does not allow us to distinguish between mechanisms. The rate-retarding affect of the electron-withdrawing trifluoromethyl substituent would support both postulates assuming that formation of the nitrenium ion in the first and the formation of the arenium ion in the second are the rate determining steps.

The observation that changes in temperature over a range of 100 °C do not substantially change the ortho/para ratio indicates that whatever mechanisms are operative have low activation energies and if two pathways are available, they have comparable energy pathways. The low activation energy precludes changing the course of the fluorination reaction easily by changing just one variable: temperature, solvent, or substituent.

In summary, it has been demonstrated that fluoroxytrifluoromethane and bis(fluoroxy)difluoromethane can be synthesized, handled, and stored in the laboratory in 100-gram quantities. The reagents are stable and provide an excellent source of fluorine. Reactions with aromatic substrates provide a synthetic method for introducing fluorine into a molecule. A preponderance of the observed

(15) Lerman, O.; Tor, Y.; Hebel, O.; Rozen, S. *J. Org. Chem.* **1984**, *49*, 806.

(16) Gassman, P. G.; Campbell, G. A. *J. Am. Chem. Soc.* **1971**, *93*, 2567.

reactions can be explained in terms of an electrophilic aromatic substitution reaction mechanism. The choice of solvent influences the ortho/para ratio for monofluorinated product with carbon tetrachloride producing an unprecedented large preference for ortho substitution in aniline derivatives. Benzene and aromatic substrates with mildly activating substituents give good yields of monofluorinated products at conversion rates of approximately 50%. Selected disubstituted aromatic substrates can be fluorinated cleanly, and FTM appears to be the reagent of choice for electrophilic substitution of fluorine on an aromatic ring in these instances.

Experimental Section

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman AccuLab 4 spectrophotometer. NMR spectra were obtained on a Varian XL-100/Nicolet TT-100 spectrophotometer. Analytical gas chromatography was performed by using a Hewlett-Packard HP5840A instrument. Liquid Chromatography was done on a Hewlett-Packard HP1084B instrument. Combination GC–MS analysis was performed on a Hewlett-Packard HP5992 instrument. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Preparation of Reagents. (a) Fluoroxytrifluoromethane (FTM). The method for synthesizing FTM consists of reacting elemental fluorine and carbon monoxide over a bed of cesium fluoride catalyst. This catalyst was prepared by melting 900 g of technical grade cesium fluoride in a 600-mL stainless steel beaker by heating with a natural gas/oxygen flame. The hot molten mass was poured into a ceramic jar and allowed to cool overnight in a dry box. It was placed on a ball mill and rotated 2 days and filtered through a No. 100 USA Standard Testing sieve (0.0059 in.) to yield 792 g of ivory colored powder of uniform size. Into a 1 × 16 in. nickel pipe, 278 g of activated CsF and 50 g of nickel helices were placed, and this catalyst reactor was connected to a gas flow system. The system allowed for the measurement of reacting gases with calibrated flowmeters, and sampling valves allowed for the analysis of products. A gas chromatograph with a 30-ft Fluorolube column was directly integrated into the system which allowed for the analysis of product at any time during the reaction. The entire flow system was passivated by slowly increasing the concentration of F_2 in a F_2/He gas mixture. In a typical experiment, carbon monoxide at a flow rate of 135 s/m (0.34 mol/h from a calibration curve) and fluorine (315 s/m, 0.691 mol/h) were added over a 2-hr, 6-min period and were mixed together before the catalyst bed in the line. A flow of helium (20 s/m) was also maintained in the fluorine line.

A highly exothermic reaction occurs to produce carbonyl difluoride which reacts further with fluorine as it passes over the catalyst. The product is collected in a gas cylinder at liquid nitrogen temperature. After transfer to a storage cylinder, FTM (66.0 g, 0.63 mol) was obtained and shown to be 96% pure by GC analysis.

(b) Bis(fluoroxy)difluoromethane (BDM). In a manner similar to the production of FTM, with the same type catalyst and the same gas flow system, BDM was produced. In a typical experiment, carbon dioxide (2.5 g, .057 mol/h) and fluorine (8.6 g, 0.23 mol/h) were combined and passed through a cesium fluoride catalyst. The gases were condensed in a metal cylinder immersed in an ethanol/liquid N_2 bath (−110 °C). After 3 h, 19.1 g (1.59 mol) of BDM was produced (93% yield, based on CO_2 as the limiting reagent) which was essentially pure as determined by GC analysis.

CAUTION! Fluorine is an extremely hazardous material because of its toxicity, corrosive nature, and strong oxidizing properties. All fittings and tubing were of monel construction, and the apparatus was degreased and pressure tested with N_2 gas and passivated with F_2 gas before reactions were run. An alumina trap was used to remove unreacted fluorine, and all organic material was excluded from the system. FTM and BDM are toxic gases, highly reactive and strong oxidizing agents. With certain solvents, noticeably ether, they react spontaneously with combustion. Excess reagent was collected in KOH traps. It is recommended that prior to any use of these reagents the investigator become familiar with the safety precautions given for use of these reagents.[17]

General Method for Addition of FTM and BDM to Aromatic Substrates. FTM and BDM can be synthesized in batch quantities and stored in gas cylinders. The experimental method used for the addition of the reagent to an organic substrate was essentially the same in all cases. The compound to be fluorinated was dissolved in an appropriate solvent and cooled to the desired temperature in a bath. FTM or BDM was bubbled into the stirred solution through a fritted glass tube. The flow of gas was measured by a Matheson mass flow meter, and the gas was bubbled through the solution for a measured length of time. The mode of addition did not appear to affect the course of the reaction. If the gas was introduced over the surface of the liquid, reaction appeared to occur at the same rate and product distribution did not change. After the addition was complete, the solution was stirred for approximately one-half hour, degassed under an aspirator, and rotary evaporated to give a product mixture that was analyzed directly, most often by gas chromatography or liquid chromatograph and at times, by ^{19}F NMR.

The mass flow of FTM and BDM may be calibrated by bubbling directly into a potassium iodide trap and titrating the iodine produced according to the following equations.

$$CF_3OF + 2I^- + 2H^+ + H_2O \rightarrow I_2 + CO_2 + 4HF$$

$$2S_2O_3^{2-} + I_2 \rightarrow 2I^- + S_4O_6^{2-}$$

A potassium iodide trap at the end of the line was used in every reaction to determine unreacted FTM or BDM not consumed by the reagent. With this method, we can determine the amount of FTM or BDM that was consumed either by reaction with the substrate or with the solvent. It should be noted at this point that FTM and BDM do react with many solvents.

There are a few good solvents characterized by high solubility and low reactivity of FTM. Most reactions were done in trifluoroacetic acid, acetic acid, carbon tetrachloride, freon, nitromethane, acetonitrile, and chloroform. However, with nitromethane, acetonitrile, and chloroform, there is a definite competition between the solvent and the substrate for FTM.

Reaction of Benzene with FTM and BDM. To a solution of 1 mL (.88 g, 11.3 mmol) benzene in 28 mL of CH_2Cl_2 at 0 °C was added FTM (9.3 mmol) over a 2 h period. The FTM was bubbled into the stirred solution through a fritted glass tube. The solution was degassed under an aspirator, *m*-fluorotoluene was added as an internal standard, and the reaction mixture analyzed directly by gas chromatography (15 ft. 10% OV 210). Analysis accounted for 100% material balance: unreacted benzene (59%), fluorobenzene (39%), 1,4-difluorobenzene (2%), and (trifluoromethoxy)benzene (2%). Quantitative analysis was done by internal standardization with known mixtures.

To a solution of 0.9 g (11.5 mmol) of benzene in 50 mL of $CFCl_3$, cooled to 0 °C and stirred with a magnetic stirrer, was added BDM through a fritted glass tube at the rate of 0.24 g/h for 3.2 h (6.35 mmol). A light straw color developed and a trace of a white insoluble solid was observed. The solution was analyzed directly by GC with *m*-fluorobenzene as an internal standard to yield 59% of recovered benzene, 28% of fluorobenzene, and 1% of 1,4-difluorobenzene which represents a material balance of 88%.

Reaction of FTM with Toluene. In a typical reaction, a solution of 0.92 g (10 mmol) of toluene was dissolved in 25 mL of $CFCl_3$ and cooled to 0 °C, and while stirring, FTM was added through a fritted glass delivery tube at the rate of 0.54 g/h for 2.2 h (11.6 mmol). The reaction mixture was directly analyzed by GC (15 ft OV-210) using $BrCCl_3$ as the internal standard. The identified products (by comparison to standard mixtures) were unreacted toluene (27%), 2-fluorotoluene (4.7%), 4-fluorotoluene (2.4%), and benzyl fluoride (6.2%). Material balance was only 40% and there were at least three unidentified peaks in the chromatogram.

Reaction of FTM with *o*-Xylene. To a solution of 1.06 g (10 mmol) of *o*-xylene in 50 mL of CH_2Cl_2 was added 1.0 g of K_2CO_3. The solution was stirred at 0 °C and FTM was added at the rate of 0.24 g/h for 5.5 h (15.6 mmol). The reaction product

(17) *Inorganic Synthesis* **1966**, *8*, 165.

was poured into H_2O and the CH_2Cl_2 extracts were combined, dried, and evaporated to yield 1.46 g of a light yellow oil. The product was analyzed by GC, NMR, and GC–MS before it turned black within 20 min. Analysis by GC (10 ft 5% Bentone + 5% SP 2100) showed *o*-xylene (13%), 4-fluoro-o-xylene (15%), and an unstable peak which disappeared as the product turned black. NMR indicated the presence of vinyl protons while GC–MS indicated two isomeric products which contained the OCF_3 group.

Fluorination of Anisole. In a typical experiment, 1.08 g (10 mmol) of anisole was dissolved in 50 mL of $CFCl_3$ in a 100-mL round bottomed flask equipped with a gas inlet tube, gas outlet tube attached to a KI trap, and magnetic stirrer. The solution was cooled to 0 °C and FTM was added at the rate of 10 cm^3/min (0.492 g/h) for 3.5 h (16.3 mmol). The black reaction mixture was degassed under an aspirator, the solvent removed on a rotary evaporator, and the residue dissolved in 100 mL of CH_2Cl_2. This solution was washed with H_2O, dried over $MgSO_4$, and filtered and the solvent evaporated to yield 1.84 g of crude product. Analysis was done by liquid chromatography with benzophenone as internal standard. (40% CH_3OH/60% H_2O, Zorbox ODS, 25-cm column). Mono-fluorinated products are available from Aldrich Chemical. Product analysis indicated that all the anisole reacted, with *o*-fluoroanisole (19%) and *p*-fluoroanisole (13%) being two of the products identified.

Synthesis of 2-Fluoro-4-(trifluoromethyl)aniline. (a) Preparation of 4-(Trifluoromethyl)acetanilide (6). *p*-Aminobenzotrifluoride, 20.5 g (0.127 mol), was dissolved in 80 mL of $CHCl_3$, and 24.05 mL (25.97 g, 0.254 mol) of acetic anhydride were added slowly and the solution was stirred for 2 h at room temperature. The ppt which formed was filtered and washed to yield 16.35 g of white solid. The fitrate was evaporated to yield 12.8 g of solid. Recrystallization from $CHCl_3$ and repeated concentration of the filtrate and recrystallizations produced 22.7 g (82%) mp 152–153.5 °C. Anal. Calcd for $C_9H_8F_3NO$:C, 53.21; H, 3.97; F, 28.05; N, 6.89. Found: C, 53.36; H, 3.99; F, 28.34; N, 6.87.

(b) Preparation of 2-Fluoro-4-(trifluoromethyl)acetanilide. To a solution of 20 g (0.099 mol) of **6** in 70 mL of acetic acid was added FTM at the rate of 1.72 g/h for 4 h then at 2.87 g/h for another 4 h. The total amount of FTM added was 0.177 mol. The reaction mixture was degassed through a KI trap, the acetic acid was rotary evaporated, and the solid produced was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried, and evaporated to yield 17.4 g of crude product. Column chromatography (350 g of silica gel, ethyl acetate–hexane 1:4) yielded 8.7 g of pure 2-fluoro-4-(trifluoromethyl)acetanilide, mp 135–7 °C. Anal. Calcd for $C_9H_7F_4NO$: C, 48.88; H, 3.19; F, 34.36; N, 6.33. Found: C, 48.93; H, 3.14; F, 34.47; N, 6.30.

(c) Hydrolysis to 2-Fluoro-4-(trifluoromethyl)aniline. A solution of 2-fluoro-4-(trifluoromethyl)acetanilide (5.5 g, 25 mmol) in 50 mL of ethanol was heated to reflux and 12.5 mL of concentrated HCl was added. After 1 h, the reaction was allowed to cool and a white ppt formed. The solvent was evaporated under reduced pressure to yield 8.78 g of white solid which was dissolved in H_2O, and $NaHCO_3$ was added. Extraction with CH_2Cl_2, drying, and evaporation of the solvent gave a liquid. Distillation at reduced pressure 55 °C (0.3 torr) yielded 3.97 g (88%) of 2-fluoro-4-(trifluoromethyl)aniline. The structure was confirmed by ^{13}C NMR comparison with an authentic sample.

Preparation of 2-(Trifluoromethyl)acetanilide (5). To a solution of 2-(trifluoromethyl)aniline, 28.0 g (0.172 mol), in 200 mL of $CHCl_3$ was added 34 mL (31.5 g, 0.31 mol) of acetic anhydride. The solution was left standing for 48 h and concentrated on a rotary evaporator to yield an oil which crystallized on standing. Recrystallization twice from hexane/$CHCl_3$ gave long, white needles. (30.0 g, 85%) mp 96–96.5 °C. Anal. Calcd for $C_9H_8F_3NO$: C, 53.21; H, 3.97; F, 28.05; N, 6.89. Found: C, 53.43; H, 4.03; F, 28.34; N, 6.87.

Competitive Rate Experiments (5 and 6). The relative rates of reaction were measured by reacting a mixture of two different acetanilides with a deficiency of FTM and analyzing the product mixture by GC. The ratio of unreacted starting materials was compared to an internal standard.

In a typical experiment, 0.2304 g (1.13 mmol) of 2-(trifluoromethyl)acetanilide and 0.2333 g (1.15 mmol) of 4-(trifluoromethyl)acetanilide were dissolved in 50 mL of TFA at 0 °C and reacted with 1.25 mmol of FTM over a 17-min period. Titration of I_2 in the KI trap indicated that a maximum of 0.48 mmol of FTM reacted. The solution was degassed and evaporated to yield a light yellow oil to which a weighed amount of benzophenone as internal standard was added and the entire mixture dissolved in 20 mL of acetone. Quantitative analysis by GC (4 ft 3% Carbowax in tandem with 6 ft 5% OV-225 column) was easily accomplished because the components were well resolved, and standard mixtures of all reactants and products were available. Analysis indicated that 94% of **5** was recovered unreacted while only 70% of **6** was unreacted with 26% identified as 2-fluoro-4-(trifluoromethyl)acetanilide product.

Addition of FTM and BDM to N-Substituted Aniline Derivatives. The data summarized in Table IV were all obtained by the same experimental procedure. A dilute solution of the substrate in a designated solvent was brought to the appropriate temperature, and FTM or BDM was bubbled into the solution through a fritted glass tube. The exit port was to a KI solution trap, and mixing was done with a magnetic stirrer. After addition of the gas, the solution was stirred for approximately 15 minutes and degassed under an aspirator and the solvent removed with a rotary evaporator to yield a crude reaction mixture. An internal standard was added and a solution of the mixture was analyzed by an appropriate analytical method. Acetanilide derivatives were analyzed by GC (3% Carbowax 20M); α,α,α-trifluoroacetanilide derivatives by GC (1:1 mixture of 5% OV-17/3% Carbowax); *N*-phenylmethane-sulfonamide derivatives by LC (NH_2 column; 15% THF/85% hexane); and *N*-phenyl-1,1,1-trifluoromethanesulfonamide derivatives by GC (10% AT-1200 + 1% H_3PO_4).

Standards for use in the analyses were prepared in a routine manner by reacting the appropriate fluoroaniline with acetic anhydride to give the acetanilides, trifluoroacetic anhydride to give the α,α,α-trifluoroacetanilides, methane sulfonylchloride to yield the *N*-phenylmethanesulfonamides, and (trifluoromethyl)sulfonic anhydride to yield the *N*-phenyl-1,1,1-trifluoromethanesulfonamides. The derivatives are summarized in Table V.

Addition of FTM to *N*-Methylacetanilide. *N*-Methylacetanilide was prepared by reacting *N*-methylaniline (14.93 g (0.191 mol) dissolved in 100 mL of $CHCl_3$) with 36 mL (0.38 mol) of acetic anhydride. The reaction temperature was controlled at 60 °C and stirred for approximately 4 h and the solvent removed to yield a crude solid product. Recrystallization from hexane gave white plates, 21.32 g (75%) mp 98–101 °C. (lit. mp 101–2 °C).[18] In a typical experiment, 0.745 g (5 mmol) of *N*-methylacetanilide was dissolved in 100 mL of $CHCl_3$, and FTM was bubbled through the solution at 0 °C for 2 h (9.24 mmol added). The brown solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to yield 0.83 g of brown liquid that was analyzed by ^{13}C NMR. The standards for analysis were prepared by reacting the appropriate fluoroacetanilide with methyl iodide and KOH.

Registry No. **5**, 344-62-7; **6**, 349-97-3; *o*-$FC_6H_4NHCOCH_3$, 399-31-5; *p*-$FC_6H_4NHCOCH_3$, 351-83-7; *o*-$FC_6H_4NHCOCF_3$, 61984-68-7; *p*-$FC_6H_4NHCOCF_3$, 35980-25-7; *o*-$FC_6H_4NHSO_2CH_3$, 98611-90-6; *p*-$FC_6H_4NHSO_2CH_3$, 35980-24-6; *o*-$FC_6H_4NHSO_2CF_3$, 23383-98-4; *p*-$FC_6H_4NHSO_2CF_3$, 23384-00-1; 2,4-$F_2C_6H_3NHCOCH_3$, 399-36-0; 2,6-$F_2C_6H_3NHCOCH_3$, 3896-29-5; 2,4-$F_2C_6H_3NHCOCF_3$, 98651-71-9; 2,6-$F_2C_6H_3NHCOCF_3$, 98634-00-5; 2,4-$F_2C_6H_3NHSO_2CH_3$, 98611-91-7; 2,6-$F_2C_6H_3NHSO_2CH_3$, 98611-92-8; 2,4-$F_2C_6H_3NHSO_2CF_3$, 23384-22-7; 2,6-$F_2C_6H_3NHSO_2CF_3$, 98611-93-9; FTM, 373-91-1; carbon monoxide, 630-08-0; 4-fluoro-*o*-xylene, 452-64-2; *o*-fluoroanisole, 321-28-8; *p*-fluoroanisole, 459-60-9; 2-fluoro-4-(trifluoromethyl)-acetanilide, 88288-14-6; 2-fluoro-4-(trifluoromethyl)aniline, 69409-98-9; 2,2,2-trifluoracetanilide, 404-24-0; *N*-phenyl-1,1,1-trifluoromethanesulfonamide, 98611-89-3; bis(fluoroxy)difluoromethane, 16282-67-0; fluorine, 7782-41-4; cesium fluoride, 13400-13-0; carbon dioxide, 124-38-9; benzene, 71-43-2; fluorobenzene, 462-06-6; toluene, 108-88-3; *o*-xylene, 95-47-6; anisole, 100-66-3; *p*-aminobenzotrifluoride, 455-14-1; 2-(trifluoromethyl)aniline, 88-17-5; acetanilide, 103-84-4; *N*-phenylmethanesulfonamide, 1197-22-4.

(18) "Dictionary of Organic Compounds", 5th ed.; Chapman and Hall: New York, 1982; entry M-00815.