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Registry No. 1, 822-87-7; *cis*-**2**, 16508-33-1; *trans*-**2**, 15175-18-5; *cis*-**3**, 63603-21-4; *trans*-**3**, 63603-22-5; (2*R**,3*R**)-**4**, 88589-61-1; (2*R**,3*S**)-**4**, 88643-63-4; **5**, 55373-58-5; **6a**, 930-68-7; **6b**, 70681-91-3; **7**, 88589-62-2; (*E*)-**8**, 88589-63-3; (*Z*)-**8**, 88589-64-4; (*E*)-*cis*-**9**, 88589-65-5; (*E*)-*trans*-**9**, 88589-66-6; (*Z*)-*trans*-**9**, 88589-67-7; (*E*)-*cis*-**10**, 88589-68-8; (*Z*)-*cis*-**10**, 88643-64-5; (*E*)-*trans*-**10**, 88643-65-6; (*E*)-*cis*-**11**, 88589-69-9; (*E*)-*cis*-**12**, 88589-70-2; (*Z*)-*cis*-**12**, 88643-66-7; (*E*)-*trans*-**12**, 88643-67-8; (*E*)-**13**, 88589-71-3; **14**, 88589-72-4; **15**, 88589-73-5; **16**, 88609-56-7; **17**, 67730-51-2; (*E*)-**18**, 88589-74-6; (*Z*)-**18**, 88589-75-7; **18** (ketone), 10276-21-8; Me_3SiCl, 75-77-4; *t*-$BuSiMe_2ONH_2$, 41879-39-4; *n*-$Bu_4N^+F^-$, 429-41-4.

Supplementary Material Available: Improved, large-scale preparations of **6** and O-(*tert*-butyldimethylsilyl)hydroxylamine are reported (5 pages). Ordering information is given on any current masthead page.

A Novel Electrophilic Fluorination of Activated Aromatic Rings Using Acetyl Hypofluorite, Suitable also for Introducing ^{18}F into Benzene Nuclei

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Acetyl hypofluorite (1) is a new compound that serves as a novel electrophilic fluorinating agent. It is special in the sense that, while it is very reactive, it is still a milder reagent than other fluoroxy compounds such as CF_3OF or CF_3COOF. It is synthesized directly from elemental fluorine and is used without any isolation or purification. The hypofluorite **1** reacts efficiently and selectively with activated aromatic rings, particularly phenol and aniline derivatives after suitable protection of the hydroxyl and the amino groups. The net result of the reaction is partly according to classical aromatic electrophilic substitution. Unlike such a substitution, however, the electrophilic fluorine atom of **1** substitutes mainly an ortho hydrogen and only occasionally small amounts of *p*-fluoro derivatives are found. Evidence supports the mechanism for this aromatic fluorination as being mainly an addition–elimination one. In many cases the electrophilic aromatic fluorinations can replace the classical 60-year-old Balz–Schiemann method, which until today is probably the most used procedure. Since aromatic fluorination with **1** is a very fast reaction and since **1** is produced directly from elemental fluorine, this is probably one of the best ways for introduction of the short-living radioisotope ^{18}F into activated aromatic rings. This will greatly encourage the synthesis of compounds suitable for use in the rapidly developing field of positron emitting transaxial tomography, which in itself depends on the efficient and easy supply of compounds possessing positron emitting isotopes.

Introducing fluorine in specific sites of aromatic rings is a very important task from both chemical and pharmaceutical points of view. Chemically, the 60-year-old Balz–Schiemann[1] method is still the most generally employed, although numerous attempts have been made in order to find more direct and convenient alternatives.[2] Oddly enough, however, although the last decades are witness to an enormous growth of organic chemistry and of the invention of most sophisticated synthetic methods, the decomposition of aromatic diazonium tetrafluoroborate salts is still the most used way of preparing fluoro aromatic compounds.

Fluorination of aromatic compounds is, of course, biologically very important as well. Pharmacologists usually replace hydrogen by the isosteric fluorine in order to elevate hydrophobicity and to retard metabolism.[3] There is also a huge interest in the pharmaceutical industry in introducing the fluorine atom into the aromatic nuclei in existing as well as in newly designed drugs. In many cases such changes proved to be very rewarding.[4]

Another most important problem is to find an efficient way to introduce ^{18}F into various aromatic nuclei. The field of positron emitting transaxial tomography (PETT) is developing today at a very rapid pace.[5] Consequently, there is a constant search for new efficient and relatively fast ways for introducing fluorine into biologically important molecules. Time, of course, is a very important factor, since the half-life of ^{18}F is about 110 min. This and the fact that the Balz–Schiemann reaction is very inefficient from a radiochemical point of view[6] have created an urgent need for developing new and fast reaction patterns not based on the use of the conventional BF_3/HF method. In the last decade several attempts have been made to introduce fluorine into aromatic nuclei by using reagents possessing electrophilic fluorine. Fluoroxytrifluoromethane, CF_3OF, was probably the most popular reagent for this purpose. It was successful in several cases, but in many others it did not produce the desired monofluoro

(1) Balz, G.; Schiemann, G. *Chem. Ber.* **1927**, *60*, 1186.
(2) See for example: Kirk, K. L. *J. Org. Chem.* **1978**, *43*, 4381. Mulvey, D. M.; DeMarco, A. M.; Weinstock, L. M. *Tetrahedron Lett.* **1978**, *19*, 1419. Hartman, G. D.; Biffar, S. E. *J. Org. Chem.* **1977**, *42*, 1468. Taylor, E. C.; Bigham, E. C.; Johnson, D. K. *J. Org. Chem.* **1977**, *42*, 362. Zweig, A.; Fischer, R. G.; Lancaster, J. E. *J. Org. Chem.* **1980**, *45*, 3597. Schack, C. J.; Christe, K. O. *J. Fluorine Chem.* **1981**, *18*, 363.
(3) "Carbon–Fluorine Compounds: Chemistry, Biochemistry and Biological Activities"; Ciba Foundation Symposium, Associated Scientific Publishers: Amsterdam, 1972.
(4) See for example: Filler, R. *Chem.-Tech. (Heidelberg)* **1974**, *4*, 752. Patrick, T. B. *J. Chem. Educ.* **1979**, *56*, 228. "Biomedicinal Aspects of Fluorine Chemistry"; Filler, R., Kobayashi, Y., Ed.; Elsevier: Amsterdam, 1982.
(5) Dagani, R. *Chem. Eng. News* **1981**, *59*(13), 30.
(6) Maximum radiochemical yields can reach 25% and in fact are much lower. See also: Ng, J. S.; Katzenellenbogen, J. A.; Kilbourn, M. R. *J. Org. Chem.* **1981**, *46*, 2520. Heinman, D. F.; Senderoff, S. G.; Katzenellenbogen, J. A.; Neely, R. G. *J. Med. Chem.* **1980**, *23*, 994. Tewson, T. J.; Welch, M. J. *J. Chem. Soc., Chem. Commun.* **1979**, 1149.

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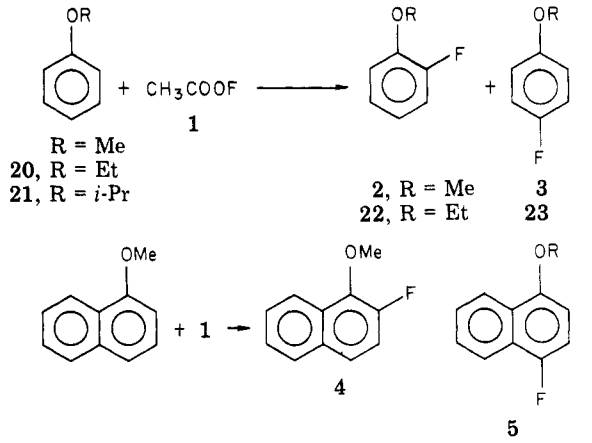
aromatic compound.[7] The very expensive xenon difluoride[8] and its interculates on graphite[9] were also employed, again only with partial success. Recently some interesting preliminary studies were also conducted with fluoroxy sulfates.[10] The reagent that could, however, be most efficient from the radiochemical point of view, namely, F_2 itself, was also examined, but on a preparative scale it proved quite inefficient.[11]

Recently we have developed and introduced acetyl hypofluorite, CH_3COOF (1), an electrophilic fluorinating agent.[12a,b] One of its advantages is its potential for introducing the ^{18}F isotope into organic molecules, since it can be prepared quickly in situ with elemental fluorine itself and then usually reacts rapidly with various substrates. In many cases this reagent is superior to F_2, CF_3OF, CF_3CF_2OF, and CF_3COOF mainly because it is a milder one. We have shown that AcOF can add itself in syn mode across olefinic bonds.[18] Soon afterward this reaction prompted one of the reagents most noticeable successes, the efficient synthesis of 2-deoxy-2-[^{18}F]fluoro-D-glucose by the Brookhaven[19] TRIUMF[20] and NIH teams, who use it for brain mapping by the PETT technique.

Remembering, however, that 1 bears an electrophilic fluorine, its scope may be wider than just reacting with double bonds. As a strong electrophile it should, as well, react fast with aromatic nuclei. If successful, such a reaction would be an important alternative to the Balz–Schiemann procedure. This would be of general importance to organic chemistry and also would constitute an efficient way for introducing radioactive fluorine into various aromatic rings. We present in this paper the results, and some of the scope and limitations, of our research in this new and important field.[21]

We found that at low temperatures of around −75 °C only activated aromatic compounds react satisfactorily with AcOF. Thus anisole produces a mixture of *o*-fluoroanisole (2) and *p*-fluoroanisole (3) in 85% yield in a ratio of 9:1, respectively. Similarly, 1-methoxynaphthalene yields in 70% a mixture of 1-methoxy-2-fluoronaphthalene (4) and 1-methoxy-4-fluoronaphthalene (5) in a ratio of 6:1.

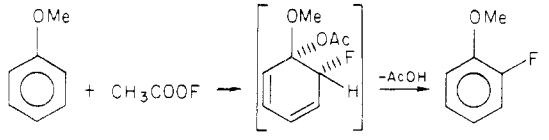


Most striking in these reactions is the unusually high ortho/para ratio. In some cases, as will be described below, even traces of a para isomer can not be found. This suggests immediately that we are not dealing here with the usual σ-complex type of substitution. There are some explanations in the chemical literature for rarely occurring reactions with such a preference for the ortho position. One of them is attack of the electrophile on the ipso position followed by its rearrangement to the ortho one.[22] Usually this leads also to some 1,4 addition of the reagent to the ring. This mechanism is not likely in our case since fluorine is not a good rearranging species and we have no evidence for any 1,4 addition to the aromatic ring. Other attempts to explain ortho substitutions were made by assuming various complexes of the electrophile with the electron-donating group of the aromatic compound, but, again, no evidence has been found for discernible complexation with the methoxy group.[23]

Although quite uncommon, addition reactions to aromatic rings are known,[7a,24] including 1,2 additions to aryl oxygen compounds across the higher electron density π region between the ipso and ortho positions.[25] If these

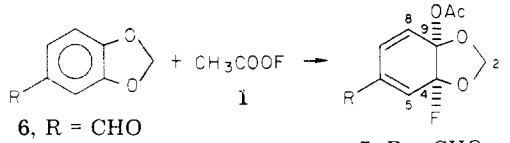
(7) (a) Patrick, T. B.; Cantrell, G. L.; Chang, C. *J. Am. Chem. Soc.* **1979**, *101*, 7434. (b) Hesse, R. H. *Isr. J. Chem.* **1978**, *17*, 60.
(8) Filler, R. *Isr. J. Chem.* **1978**, *17*, 71.
(9) Agranat, I.; Rabinovitz, M.; Selig, H.; Lin, C. H. *Synthesis* **1977**, 267. Selig, H.; Rabinovitz, M.; Agranat, I.; Lin, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 953.
(10) (a) Stavber, S.; Zupan, M. *J. Chem. Soc., Chem. Commun.* **1981**, 148. (b) Ip, D. P.; Arthur, C. D.; Winans, R. E.; Appelman, E. H. *J. Am. Chem. Soc.* **1981**, *103*, 1964.
(11) Cacace, F.; Giacomello, P.; Wolf, A. P. *J. Am. Chem. Soc.* **1980**, *102*, 3511.
(12) (a) Lerman, O.; Rozen, S. *J. Org. Chem.* **1983**, *48*, 724. (b) The terms "electrophilic fluorine" and "electrophilic fluorination" have lately raised some dispute among chemists. This dispute is based upon several works, among them the interesting synthetical publication of Des Marteau[13] and of some remarks by Christe.[14] It seems to us that there is a place for some clarification on this subject. An electrophilic fluorinating agent is by no means a molecule with partially positive fluorine. Such a reagent, however, should consist of a highly electronegative, good leaving group, which is weakly bonded to the fluorine atom. In the ground state it should possess the smallest possible dipole moment as, for example, $FClO_3$:0.023D.[15a] The electronegativity of the TeF_5O group was evaluated to be 3.87,[16] and it is reasonable to assume that SF_5O and CF_3O groups will be close to, or will even surpass, this value, so the respective compounds (SF_5OF, CF_3OF, etc.) will be almost unpolarized. When an electron-rich center becomes associated with such a molecule in the transition state, the part of the fluoroxy reagent with the higher electron affinity will be attracted to it, causing a concerted ejection of the good leaving group. No deficiency of electrons need thus develop about the fluorine atom and the overall reaction can be expressed as follows[7b] (X = electron-rich center): $R-X + F-Y \rightarrow R-X^+-F + Y^-$. Des Marteau in his work[13] reached a conclusion that CF_3OF does not react as an electrophile but as a radical agent. This is correct in that special case, since he employs electron-poor olefins, anaerobic conditions, and, most important, very high (sometimes 100%) concentration of the substrate in low polarity solvents. Such conditions will favor radical chain reactions. This does not mean, however, that the results of many earlier works with fluoroxy compounds (ref 7 and references therein, 21, 27, to name a few) should not be explained by an electrophilic fluorination mechanism, since they all employed conditions that depress radical reactions and since this is the only mechanism compatible with the results.[7b] The conclusion of Christe,[14] based on physical and spectroscopic data, is that all fluoroxy reagents in their ground state are not polarized so as to place a partial positive charge on the fluorine. This is true of course, and indeed it is probably a "misconception" to postulate a positively polarized fluorine, but as we have mentioned above, no such requirement is needed for an electrophilic fluorinating reaction. Thus it seems that fluoroxy reagents, and for that matter F_2 as well,[17] may react in either radical or electrophilic mode, depending very much on the substrates and the conditions of the reactions.
(13) Johri, K. K.; Des Marteau, D. D. *J. Org. Chem.* **1983**, *48*, 242.
(14) Christe, K. O. *J. Fluorine Chem.* **1983**, *22*, 519.
(15) (a) "Handbook of Chemistry and Physics", 62nd ed.; Weast, R. C., Ed.; CRC Press: Boca Raton, FL, 1981–1982; p E-60. (b) *Ibid.*, p E-64.
(16) Birchall, R.; Myers, R. D.; De Waard, H.; Schrobilgen, G. J. *Inorg. Chem.* **1982**, *21*, 1068.
(17) Rozen, S.; Gal, C.; Faust, Y. *J. Am. Chem. Soc.* **1980**, *102*, 6860.
(18) Rozen, S.; Lerman, O.; Kol, M. *J. Chem. Soc., Chem. Commun.* **1981**, 443.
(19) Shiue, C. Y.; Salvadori, P. A.; Wolf, A. P.; Fowler, J. S.; MacGregor, R. R. *J. Nucl. Med.* **1982**, *23*, 899.
(20) Adam, M. J. *J. Chem. Soc., Chem. Commun.* **1982**, 730.
(21) For a preliminary communication, see: Lerman, O.; Tor, Y.; Rozen, S. *J. Org. Chem.* **1981**, *46*, 4629.
(22) Moodie, R. B.; Schofield, K. *Acc. Chem. Res.* **1976**, *9*, 287. Banwell, T.; Morse, C. S.; Myhre, P. S.; Vollmar, A. *J. Am. Chem. Soc.* **1977**, *99*, 3042.
(23) Misaki, S. *J. Fluorine Chem.* **1981**, *17*, 159. Lynch, B. M.; Chen, C. M.; Wigfield, Y. Y. *Can. J. Chem.* **1968**, *46*, 1141. Hartshorn, S. R.; Moodie, R. B.; Schofield, K. *J. Chem. Soc. B* **1971**, 2459.
(24) De la Mare, P. B. D. *Acc. Chem. Res.* **1974**, *7*, 361. Fischer, A.; Rodberger, R. *J. Chem. Soc., Chem. Commun.* **1975**, 798.

reactions are followed by elimination, the net result can be seen as an electrophilic substitution. We believe that this is the case with the reaction of our hypofluorite **1** with the activated aromatic rings.



2

In order to test the addition–elimination hypothesis, we decided to react **1** with such an aromatic compound where elimination of the elements of AcOH from an adduct, if formed, would not be possible. Such a compound should possess two vicinal activating groups to ensure addition between them and should neither be easily oxidized nor possess good leaving groups. Piperonal (**6**) offers such features, and, indeed, when a large excess[26] of it was reacted with **1**, the adduct **7** was isolated in 55% yield. Its properties are in full agreement with the proposed structure. It is worth pointing out, however, that the suggested

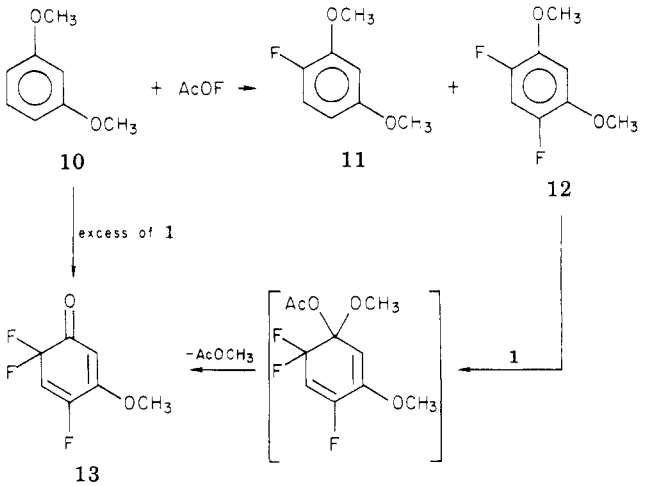


6, R = CHO
8, R = H

7, R = CHO
9, R = H

stereospecifity is based on the fact that AcOF and CF_3C-OOF add themselves across double bonds in a practically exclusive syn manner[18,27] and that in **7** any other configuration will lead to a highly strained structure. The proof for the regiospecifity of this reaction is based on the fact that the aldehydic proton appears as a doublet in the NMR spectrum (J = 0.6 Hz). Such $^5J_{HF}$ are known, as is evident also from this work, where in some cases the methyl group of various fluoroanisoles appears as a doublet ($^5J_{HF}$ = 0.4–0.7 Hz). The UV spectrum—λ_{max} 267 nm (ϵ 1650)—is also in excellent agreement with the cyclohexadiene structure. It should be noted here that the addition is faster than the oxidation of the aldehyde, so this relatively sensitive group was not affected.[28] The same type of adduct, **9**, was formed when 1,2-(methylenedioxy)benzene (**8**) itself was reacted although in 32% yield only. The lower yield here is not surprising since this compound does not benefit from the deactivating effect of the aldehyde group present in **6** on the double bonds.

When 1,3-dimethoxybenzene (**10**) was reacted with **1**, two compounds were isolated, 1-fluoro-2,4-dimethoxybenzene (**11**) in 40% yield and 1,5-difluoro-2,4-dimethoxybenzene (**12**) in 55% yield. The site of the substitution can easily be determined mainly by the NMR spectrum. It seems that steric effects prevent the addition of **1** to the 1,2 or 2,3 π bonds, which would have resulted in introduction of the fluorine between the two methoxy groups. When excess of **1** was used, the yield of **12** was increased at the expense of **11** and the ratio of **12**/**11** was more than 2. If a still larger excess of **1** was employed or if **12** itself was subjected to fluorination, the aromaticity was destroyed and the corresponding cyclohexadienone **13** was obtained. The formation of **13** can only be explained by addition of AcOF across the π bond of the two sp^2 carbons bearing the methoxy and fluorine groups. This adduct, however, can not eliminate the elements of AcOH, and in order to stabilize itself, it eliminates the elements of methyl acetate. It should be noted, of course, that although fluorine is a very electronegative atom, it is quite small and a back-donation of its lone pair is possible so it has little effect on the electron density of the double bond. This contributes, of course, to the ease of the above addition of **1** to **12**, leading to **13**. In general, the selective fluo-



10 **11** **12**

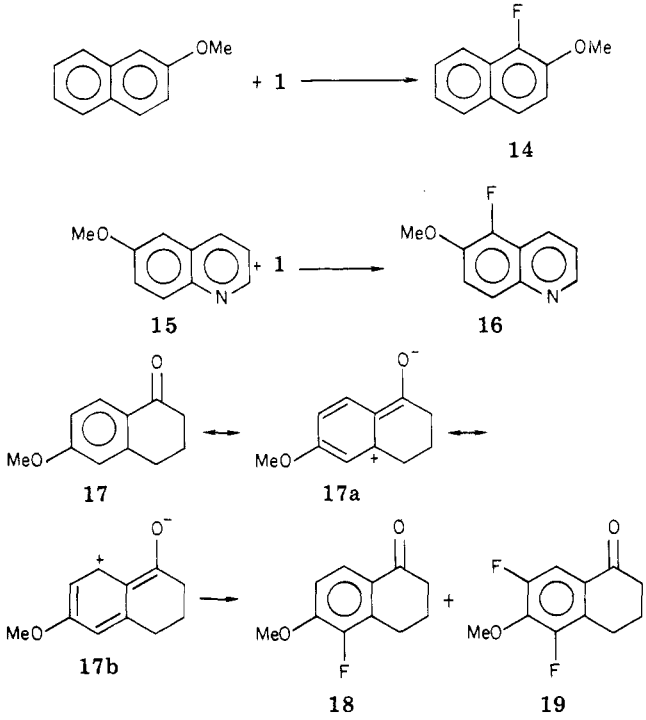
13

rination achieved by the reaction of **1** with aromatic compounds is in accordance with the electron density of the various sites in the aromatic molecule. This can be demonstrated with 2-methoxynaphthalene, which in reaction with **1** gives only 1-fluoro-2-methoxynaphthalene (**14**) in 65% yield. The same situation is present in 6-methoxyquinoline (**15**). Since the 5,6 bond of this molecule is more electron rich than the 6,7 bond, the AcOF adds itself to it and the only monofluorinated product obtained was the 5-fluoro-6-methoxyquinoline (**16**) in 75% yield. The identification of **16** is mainly based on the fact that only small $^5J_{HF}$ coupling constants are found, as is evident also from the ^{19}F NMR spectrum. The ^{19}F NMR spectrum offers additional support, since the signal at −147 ppm is a characteristic one for fluorine situated ortho to methoxy and at an α position to a second condensed aromatic ring, as in **14**. It is worth noting that the heteroatom, although possessing a free lone pair of electrons, was not attacked by the acetyl hypofluorite electrophilic fluorine.[29]

6-Methoxy-1-tetralone (**17**) serves as an additional example of the selectivity of the fluorination which is based on the degree of activation of the various π regions. Among the charged resonance structures of **17**, **17a** will obivously contribute more than **17b**, which means higher electron density between carbons 5, 6 than carbons 6, 7. Indeed, the major fluorinated product was 5-fluoro-6-methoxy-1-tetralone (**18**). It identification rests in part on the aromatic region of its NMR spectrum, which shows a signal at 7.84 ppm for proton 8 (dd, J_{HH} = 8.5 Hz, $^5J_{HF}$ = 1.6 Hz) and at 6.91 ppm for proton 7 (t, $^4J_{HF}$ = J_{HH} = 8.5 Hz). The fluorine atom resonates at −140.5 ppm as a doublet ($^4J_{HF}$ = 8.5 Hz). Only traces of the 7-monofluoro isomer were found. In this reaction we have isolated an additional

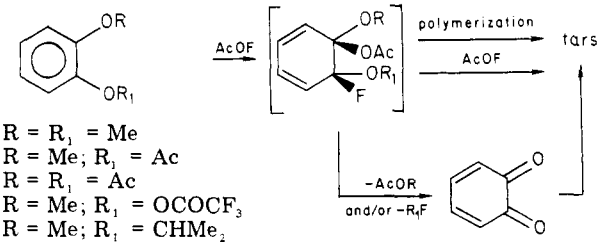
(25) Brown, R. D. *Tetrahedron, Suppl.* **1963**, *19*, 337.
(26) In this case the conversion is deliberately kept low (25%) to minimize the fast reactions of the reactive cyclohexadiene system with excess of the reagent.
(27) (a) Rozen, S.; Lerman, O. *J. Org. Chem.* **1980**, *45*, 672. (b) Lerman, O.; Rozen, S. *Ibid.* **1980**, *45*, 4122.
(28) We have found that aromatic aldehydes are only slowly oxidized by a variety of electrophilic fluorinating agents, and frequently the products are acyl fluorides. We are trying now to understand the mechanism and estimate the scope of this unusual reaction.
(29) We are studying now in more detail the electrophilic fluorination of several heterocyclic aromatic systems and hope to publish the results of this study soon.

compound obtained in lower yield and which was identified as 5,7-difluoro-6-methoxy-1-tetralone (**19**). Its formation may indicate that when there are no steric effects that force **1** to add across the π bond between the methoxy and the fluorine, as in **13**, it prefers to add across the other π bond, leading to an *o,o'*-difluoromethoxy system. It is seen



that the addition–elimination reaction of AcOF, which results eventually in fluoroaromatic substitution, is more sensitive to steric effects than the traditional electronic one. This is further demonstrated by ethoxybenzene (**20**) and isopropoxybenzene (**21**). When **20** reacts with acetyl hypofluorite, only 50% conversion was achieved and of this only 46% of the *o*-fluoroethoxybenzene (**22**) was isolated along with an additional 6% of the para isomer **23**. Both the conversion and the yield of the *o*-fluoro product are considerably lower compared to that of anisole. The even more hindered **21** practically does not react, and only traces of ortho and para fluorination were detected by ^{19}F NMR. The sensitivity of **1** to the relatively small differences in electron densities, that usually are responsible for the good regiospecificity of the reaction, has also some disadvantages, as in the reaction of 1,2-dimethoxybenzene (**24**) with the hypofluorite **1**. The reaction was practically instantaneous and it did not matter at what level the conversion was kept, or if the aromatic substrate was introduced to the reagent or vice versa, the results were always the production of tars and no definite monofluoro compounds were detected. The crude reaction mixture exhibited carbonyl absorptions in the IR, acetates in the NMR, and various fluorine atoms in the ^{19}F NMR spectrum. Such results, together with a large amount of polymeric substances, support the proposed mechanism. The AcOF adds itself across the most activated π region—between the two oxygens, but then, there is no easy way for elimination and the reactive cyclohexadiene derivative can be polymerized, react very fast with the reagent that is still present, or decompose to give various quinones.

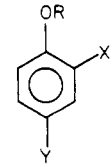
We found that phenyl acetate does not react with AcOF, apparently because of insufficient activation of the ortho positions. We then tried to moderate the electron donation effect in 1,2 dioxy derivatives by substituting methoxy



24, R = R_1 = Me
25, R = Me; R_1 = Ac
26, R = R_1 = Ac
27, R = Me; R_1 = $OCOCF_3$
28, R = Me; R_1 = $CHMe_2$

groups by acetate as in 1-methoxy-2-acetoxybenzene (**25**), 1,2-diacetoxybenzene (**26**), or even 1-methoxy-2-(trifluoroacetoxy)benzene (**27**). However, the disappearance of the starting materials was in all cases very fast, and only tars were obtained. No different results were observed when 1-methoxy-2-isopropoxybenzene (**28**) served as a substrate although as earlier described, the isopropoxy group in **21** prevented the reaction there. On the other hand, even a strong deactivating moiety would not overcome the activating effect of the methoxy group. Thus if one of the ortho positions to the methoxy is occupied by a nitro group as in 2-nitroanisole (**29**), the AcOF will attack the second ortho position, leading to 2-nitro-6-fluoroanisole (**30**). An equally successful fluorination was observed when 4-nitroanisole (**31**) was converted to 2-fluoro-4-nitroanisole (**32**).

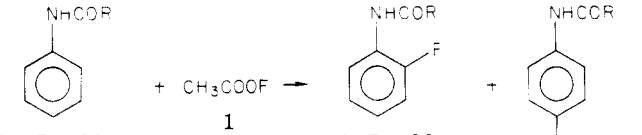
It seems that etherification of the aromatic oxygen function is practically the only way to activate the ring to such an extent that the AcOF will be able to add itself across the ipso and ortho positions. Is it necessary, however, to protect the free hydroxyl group? Usually, the answer is positive and phenol itself produces mainly tars since it is easily oxidized and the resulting cyclohexadiene system reacts immediately with the excess of the reagent, or undergoes polymerization. If, however, a strong deactivating group is present in the molecule, the hydroxyl may survive the oxidative conditions. Thus 4-nitrophenol (**33**) was fluorinated to produce directly the 2-fluoro-4-nitrophenol (**34**) in 56% yield. Even when the deactivated group is not as strong as the nitro one, as in methyl salicylate (**35**), the *o*-fluoro **36** and the *p*-fluoro **37** derivatives could be isolated, although in low yields and in ratios slightly favoring para substitution.



29, R = Me; X = NO_2; Y = H
30, R = Me; X = NO_2, Y = H, F at 6-position
31, R = Me; X = H; Y = NO_2
32, R = Me; X = F; Y = NO_2
33, R = H; X = H; Y = NO_2
34, R = H, X = F; Y = NO_2
35, R = H; X = COOMe; Y = H
36, R = H; X = COOMe; Y = H, F at 6-position
37, R = H; X = COOMe; Y = F

Oxygen is not the only activating atom that enables the acetyl hypofluorite to react with the aromatic ring in the addition–elimination mode. We found that aniline derivatives are also excellent substrates for this reaction. As in the case of phenol, aniline, *N*-methylaniline, and *N,N*-dimethylaniline cannot survive the treatment with the electrophilic fluorine present in the AcOF, since it readily attacks the nitrogen lone-pair electrons. This can be easily overcome by acetylating the aromatic amino group. Thus acetanilide (**38**) reacts with **1** to give a very similar mixture to the one obtained from the reaction of **1** and anisole. The

o-fluoroacetanilide (**39**) was obtained in 50% yield, while the yield of the *p*-fluoro derivative (**40**) did not exceed 7%. Using trifluoroacetanilide (**41**) or pivalanilide (**42**) did not prevent **1** from reacting with the aromatic ring despite the electron-withdrawing or the bulky group located on the nitrogen. In these two cases we have been able to isolate in good yields only the *o*-fluoro derivatives **43** and **44**.

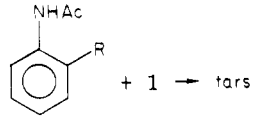


38, R = Me
41, R = CF_3
42, R = CMe_3

39, R = Me
43, R = CF_3
44, R = CMe_3

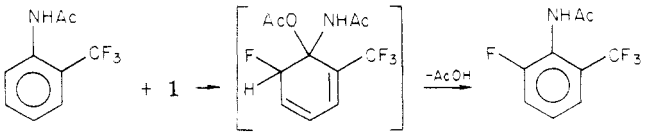
40, R = Me

Additional support for the addition–elimination mechanism is offered by certain aniline derivatives with ortho substituents. If these are electron-donating substituents, then the region between the carbons bearing the nitrogen and the substituent will have the highest electron density. Acetyl hypofluorite will attack this region, but easy elimination of the elements of AcOH would not be possible and the resulting reactive cyclohexadiene derivative will react with the excess of the reagent or polymerize to give undefined products. This is indeed the case with *o*-methyl- or *o*-bromoacetanilide.



R = Me, Br

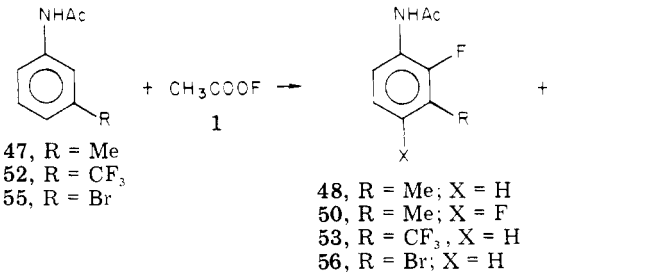
If on the other hand, an electron-withdrawing group is located in the ortho position like *o*-(trifluoromethyl)-acetanilide (**45**), the reagent will attack the second ortho position, resulting eventually in 2-(trifluoromethyl)-6-fluoroacetanilide (**46**) in good yield. When the electron-



45 **46**

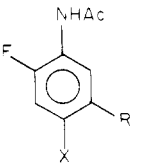
donating group was moved from the ortho to the meta or the para position, then of course elimination could take place. The corresponding fluoro derivatives were easily formed, isolated, and identified. *m*-Methylacetanilide (**47**) produces the two possible fluoro derivatives ortho to nitrogen **48** and **49** in equal amounts, along with two additional minor components, which proved to be the corresponding difluoro compounds **50** and **51**. It should be noted that the second fluorine is in the para position to the nitrogen (see Experimental Section). No such difluoro compounds were found when the trifluoromethyl group replaces the methyl as in **52**. In this case only the two possible *o*-fluoro isomers **53** and **54** were formed again in 1:1 ratio and practically in the same yields as for the methyl derivative **47**.

This is also true for *m*-bromoacetanilide, which unlike the ortho isomer reacts cleanly with **1** to produce the two ortho isomers **56** and **57**. In an analogous way, when two electron-donating groups occupy both ortho positions as in 2,6-dimethylacetanilide, the reaction with **1** produces only tars, but when both methyl groups are moved to meta positions as in **58**, the addition–elimination reaction can take place and 2-fluoro-3,5-dimethylacetanilide (**59**) was the only product isolated in 67% yield.

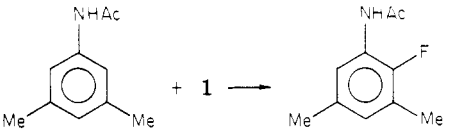


47, R = Me
52, R = CF_3
55, R = Br

48, R = Me; X = H
50, R = Me; X = F
53, R = CF_3, X = H
56, R = Br; X = H

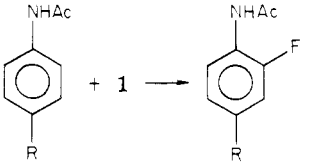


49, R = Me; X = H
51, R = Me; X = F
54, R = CF_3, X = H
57, R = Br; X = H



58 **59**

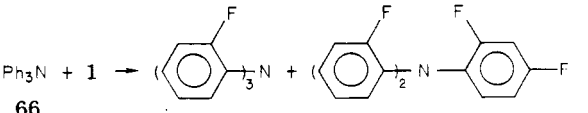
It should be noted that, unlike the case of *m*-dimethoxybenzene (**10**), fluorine can replace hydrogen in position 2 of the meta-substituted anilides. While this position is electronically more activated toward electrophilic attack in both cases, the steric hindrance from the two methoxy groups is greater here than in any of the above 3-substituted anilides. Therefore, acetyl hypofluorite, which is sensitive to such steric factors (see the reaction with **20** and **21**), can react in this series of compounds with the part of the π region situated between the two 1,3-substituents. The fluorination is effective also when the weak electron-donating or electron-withdrawing groups are located in the para position like in compounds **60–62**. In such cases good to very good yields of the corresponding *o*-fluoroacetanilide derivatives **63–65** were obtained and no difluoro compounds were detected.



60, R = Me
61, R = CF_3
62, R = Br

63 (85%)
64 (72%)
65 (65%)

As we have stated, the amino group usually should be protected, otherwise the electrophilic fluorine attacks this atom, producing unstable nitrogen fluorine compounds, which easily decompose, leading eventually to tars. If, however, the basicity of the nitrogen is sufficiently low as in triphenylamine (**66**), the electrophilic fluorine attacks the activated aromatic rings and tris(2-fluorophenyl)amine (**67**) can be isolated in 30% yield along with a smaller amount of *N*,*N*-bis(2-fluorophenyl)-2,4-difluorophenylamine (**68**) (11% yield).



66 **67** **68**

While the above results are concordant with the dominant ortho fluorination of activated aromatic rings, the problem concerning the source of the minor *p*-fluoro derivatives that are found in some cases still remains. It seems to us that along with the addition–elimination process, the more conventional electrophilic aromatic substitution via the corresponding σ complex also takes place, leading to para substitution as well. This should not be surprising because AcOF, although not strongly electrophilic relative to other fluoroxy compounds, is still a powerful electrophile. The existance of this less important orthodox electrophilic substitution is also supported by the fact that compounds that are relatively deactivated to this mechanism like **29**, **41**, **45**, **52**, and **55**, or compounds in which the para position is sterically hindered, like **58**, do not produce any detectable amount of para derivatives. Toluene is also an interesting case. Its reaction with **1** is relatively very slow, and after 2 h only 50% of the reactants disappeared. This is in sharp contrast to the few seconds to few minutes required for the other aromatic compounds to react. Furthermore, most of the reacted toluene was converted to an unseparable mixture, and the only isolable monofluoro compounds were *o*- and *p*-fluorotoluenes in yields of about 10% each. It is worth noting that the ^{19}F NMR of the crude mixture shows that the methyl group was also fluorinated to some extent. Since the electron density near the methyl group is not as high as in anisoles and anilines, the addition–elimination reaction is not likely to take place and the more usual electrophilic substitution is executed by the oxygen-bound fluorine. This leads to about a 1:1 ratio of the para and ortho isomers, and since this reaction is relatively slow, there is enough time for the oxidizing media to produce considerable amounts of tar.

In conclusion, a novel fluorinating method, with a novel reagent was developed for activated aromatic compounds. Although some points are still unresolved, as in the attempts to fluorinate vicinal dimethoxyarene, this method and reagent exhibit quite a few advantages over the other fluorinating agents possessing oxygen-bound fluorine. The method is easy to execute, once one has assembled a simple fluorine line. Moreover, there is no need to introduce an extra amino group that requires diazotation to sometimes explosive diazofluoroborates, as in the classical Baltz–Schiemann procedure. Probably most important, however, is that this method is based on using elemental fluorine, is fast, and is regioselective, features that are highly desirable for efficient introduction of labeled fluorine into biologically active compounds for use in the rapidly developing positron emitting transaxial tomography technique.

Experimental Section

^1H NMR spectra were recorded with a Bruker WH-90 spectrometer at 90 MHz with $CDCl_3$ as the solvent and Me_4Si as an internal standard, while ^{19}F spectra were measured at 84.67 MHz and are reported in parts per million upfield from $CFCl_3$, which also served as the internal standard. ^{13}C NMR were measured with the same instrument at 22.63 MHz with Me_4Si as internal standard. Mass spectra were measured with a Du Pont 21-491B spectrometer. IR spectra were recorded as neat films on a Perkin-Elmer 177 spectrometer.

General Fluorination Procedure. A description of the setup and the procedures for working with elemental fluorine has previously been described.[27a] However, before working with fluorine and AcOF, it is nessary to repeat[12a] a word of caution.

Caution: Fluorine and acetyl hypofluorite should be treated with care since they are strong oxidizers. The work should be conducted in an efficient hood or in a very well-ventilated area. The toxicity of acetyl hypofluorite is not known yet, but some of the oxyfluoro reagents like CF_3OF are known to be strong poisons. If elementary precautions are taken, work with fluorine and its fluoroxy derivatives is safe and relatively simple. In the past, we have never had any explosions or accidents while working with fluorine.

Preparation of AcOF (1) and Methods of Reaction. About 10% of fluorine in nitrogen was bubbled through a suspension of 8 g of sodium acetate in 400 mL of solvent [$CFCl_3$/AcOH (10:1)] at −75 °C by using an efficient vibromixer.[27a] The progress of the reaction was monitored by treating aliquots with KI and titrating the liberated iodine.

The reaction was carried out either by adding a cold (−75 °C) $CH_2Cl_2/CFCl_3$ solution of the substrate to the reaction vessel that contained the acetyl hypofluorite (method A) or by transferring **1** by a stream of nitrogen to another vessel that contained the cold solution of the aromatic compound (method B), thus ensuring an excess of the substrate over the hypofluorite. In most cases both methods gave the same results, but in a few cases method B resulted in cleaner reaction mixtures. When working according to method A, the AcOF was usually in an excess of about 10–50% over the substrate unless otherwise stated and usually there was no practical way to monitor the fast reactions. Only working according to method B presented the opportunity to monitor the reaction and usually it was stopped when 80–90% conversion was achieved. In cases when the conversion was not full, the reported yields were based on the consumed starting material. The reactions were usually carried out on scales of 20–40 mmol. The term "worked up as usual" means stopping the reaction by pouring it into 500 mL of water, washing the organic layer with $NaHCO_3$ solution and then water until neutral, drying over $MgSO_4$, and evaporating. The crude product was usually purified by chromatography on a short silica gel column and, if needed, also by high-pressure liquid chromatography (LiChrosorb si 60, Merck). Unless a melting point is given, the products are liquids.

Only unpublished physical data for the fluorine-containing compounds are given in this section. Microanalyses also confirm the correct composition of the new fluorinated compounds.

Fluorination of Anisole. Method A: 80% conversion; **2** and **3** were separated by HPLC, using 25% EtOAc in cyclohexane, yields 77% and 8%, respectively. All physical data are in accordance with the literature.[30] **2**: ^{19}F NMR −136 ppm. **3**: ^{19}F NMR −124.9 ppm.

Fluorination of 1-Methoxynaphthalene. Method A: full conversion; **4** was obtained in 62% yield:[10a] NMR δ 7.21–8.25 (6 H, m), 4.10 (3 H, d, $^5J_{HF}$ = 2.2 Hz, OCH_3); ^{19}F NMR −134 ppm (br s). The para isomer **5** was also obtained in 8% yield, although not in analytical purity: ^{19}F NMR −124 ppm.

Fluorination of Piperonal (6). Method B. The conversion was kept low: 25%. The crude product was homogenized by HPLC, using 18% EtOAc in cyclohexane as eluent. The adduct **7** was isolated in 55% yield (based on the reacted starting material): IR 1740, 1695 cm^{-1}; UV (CH_3CN) λ_{max} 267 nm (ϵ 1650); MS, m/e 228 (M^+), 200 ($M - CO)^+$, 169 ($M - OAc)^+$; NMR δ 9.64 (1 H, d, $^5J_{HF}$ = 0.6 Hz), 6.86 (1 H at 5, dd, $^3J_{HF}$ = 6 Hz, $^4J_{HH}$ = 0.8 Hz), 6.67 (1 H at 7, dd, J = 10 Hz, $^4J_{HH}$ = 0.8 Hz), 6.18 (1 H at 8, dd, J = 10 Hz, $^4J_{HF}$ = 3.8 Hz), 5.31 and 5.00 (1 H each at 2, $^4J_{HF}$ = 2.6 Hz, $^4J_{HF}$ = 1.2 Hz, respectively), 2.09 (3 H, s, acetate); ^{19}F NMR −117.1 ppm; ^{13}C NMR 190 (aldehyde), 168.2 (ester, carbonyl), 136.3 (C-5, d, $^2J_{FC}$ = 37 Hz), 136.0 (C-6), 127.3 (C-8), 118.7 (C-7), 108.1 (C-4, d, $^1J_{FC}$ = 238 Hz), 103.6 (C-9, d, $^2J_{FC}$ = 22 Hz), 90.8 (C-2), 20.8 ppm (methyl).

Fluorination of 8 was carried out similarly to that of **6** (20% conversion), using 12% EtOAc in cyclohexane as eluent. The adduct **9** was isolated in 32% yield: IR 1740 cm^{-1}; UV (CH_3CN) λ_{max} 249 nm (ϵ 3700); MS, m/e 200 (M^+), 141 ($M - OAc)^+$; NMR δ 6.11–6.19 (m, 4 H, vinylic protons), 5.18 (1 H, d, $^4J_{HF}$ = 2.4 Hz, one of the methylene protons), 4.90 (1 H, br s, the second methylene proton), 2.05 (3 H, s, acetate protons); ^{19}F NMR −116.5 ppm; ^{13}C NMR 108.0 ppm (d, $^1J_{CF}$ = 248 Hz). Anal. Calcd for $C_9H_9FO_4$: C, 54.0; H, 4.5. Found: C, 53.9; H, 4.6.

Fluorination of 1,3-dimethoxybenzene (10) was carried out according to method B and monitored by GC. When the con-

(30) Gutowsky, H. S.; McCall, D. W.; Stolberg, V. C. *J. Am. Chem. Soc.* **1965**, *87*, 678.

version reached 90–95%, the reaction was stopped and chromatographed on silica, using 12% EtOAc in cyclohexane as eluent. The monofluoro derivative **11**[31] was eluted first in 39% yield: MS, m/e 156 (M^+), 141 ($M - CH_3)^+$, 125 ($M - OCH_3)^+$; NMR δ 6.96 (1 H at 5, dd, J_{HH} = 8.8 Hz, $^3J_{HF}$ = 11.2 Hz), 6.26–6.57 (2 H, m), 3.85 and 3.76 (3 H each, two methoxy groups, s); ^{19}F NMR −146.4 ppm. The difluoro compound **12** was eluted next: a solid, mp 99 °C (from hexane); yield 55%; MS, m/e 174 (M^+), 159 ($M - CH_3)^+$, 143 ($M - OCH_3)^+$; NMR δ 6.90 (1 H at 5, t, $^3J_{HF}$ = 10.9 Hz), 6.63 (1 H at 2, t, $^4J_{HF}$ = 7.9 Hz), 3.88 (6 H, s, two methoxy groups); ^{19}F NMR −141.9 ppm. Anal. Calcd for $C_8H_8F_2O_2$: C, 55.13; H, 4.60. Found: C, 54.88; H, 4.68. The 4,6,6-trifluoro-3-methoxy-2,4-cyclohexadienone (**13**) was obtained in traces in this reaction, but when 4-fold excess of **1** was employed by using the fluorinating method A or when **12** was a substrate, **13** was isolated in 20–25%. It can be crystallized from hexane, but attempts to measure its melting point failed since it decomposed at 37 °C: IR 1610, 1660 cm^{-1}; UV (hexane) λ_{max} 224 nm (ϵ 1.1 × 10^4), 294 (ϵ 4.1 × 10^3); MS, m/e 178 (M^+), 159 ($M - F)^+$; NMR δ 6.28 (1 H at 5, dt, $^3J_{HF}$ = 6.2 Hz, $^3J_{HF}$ = 9.4 Hz), 5.59 (1 H at 2, dt, $^4J_{HF}$ = 6.2 Hz, $^4J_{HF}$ = 3.5 Hz), 3.91 (3 H, s, methoxy); ^{19}F NMR −101.4 (2 F), −123.1 ppm (1 F).

Fluorination of 2-methoxynaphthalene by method A yields after chromatography with 6% EtOAc in PE 65% of the monofluoro derivative **14**, which is known in the literature:[10a] ^{19}F NMR −147.8 ppm.

Fluorination of 6-methoxyquinoline (15) was executed by method A; full conversion; the fluoro derivative **16** was purified by chromatography (30% EtOAc in PE) and by crystallization from EtOH; mp 40 °C; yield 74%. In the past there was an abortive attempt to prepare this compound by the Skraup reaction:[32] MS, m/e 177 (M^+), 162 ($M - CH_3)^+$; NMR δ 8.82 (1 H at 2, dd, J_1 = 4.0 Hz, J_2 = 1.5 Hz), 8.37 (1 H at 8, dd, J_{HH} = 8.0 Hz, $^5J_{HF}$ = 0.5 Hz), 7.95–7.27 (3 H, m), 4.05 (3 H, methoxy group, d, $^5J_{HF}$ = 0.6 Hz); ^{19}F NMR −147 ppm.

Fluorination of 6-Methoxy-1-tetralone (17). Method A: conversion of 85%. The oily crude was subjected to high-pressure chromatography, using 20% EtOAc in cyclohexane. The monofluoro compound **18** was eluted first and crystallized from MeOH: mp 86 °C (53% yield); IR 1660 cm^{-1}; MS, m/e 194 (M^+), 166 ($M - CO)^+$; NMR δ 7.84 (1 H at 8, dd, J_{HH} = 8.6 Hz, $^5J_{HF}$ = 1.6 Hz), 6.91 (1 H at 7, t, J_{HH} = $^4J_{HF}$ = 8.0 Hz), 3.94 (3 H, OMe, s); ^{19}F NMR −140.5 ppm (d, $^4J_{HF}$ = 8.0 Hz). Anal. Calcd for $C_{11}H_{11}FO_2$: C, 68.04; H, 5.67. Found: C, 68.26; H, 5.87. The difluoro derivative **19** was eluted next: mp 63 °C (from hexane, 13% yield); IR 1660 cm^{-1}; MS, m/e 212 (M^+), 197 ($M - CH_3)^+$, 184 ($M - CO)^+$; NMR δ 7.58 (1 H at 8, dd, $^3J_{HF}$ = 11.6 Hz, $^5J_{HF}$ = 1.8 Hz), 4.09 (3 H, OMe, t, $^5J_{HF}$ = 1.7 Hz); ^{19}F NMR −131 (1 F), −132.7 ppm (1 F). Anal. Calcd for $C_{11}H_{10}F_2O_2$: C, 62.26; H, 4.72. Found: C, 62.03; H, 4.64.

Fluorination of Ethoxybenzene (20). Method A: conversion of 50%. The yield of the known *o*-fluoro isomer **22** was 46% (^{19}F NMR −135.3 ppm) and that of the para isomer **23** 6% (^{19}F NMR −124.9 ppm).

Fluorination of 2-nitroanisole (29) and 4-nitroanisole (31) was performed by method A and B, respectively. The known products **30**[33] and **32**[34] were obtained in 42% yield: ^{19}F NMR −127 ppm and 47% yield and ^{19}F NMR −131.4 ppm, respectively.

Fluorination of phenol derivatives was performed according to method B. The known[34] 2-fluoro-4-nitrophenol (**34**) was obtained in 62% yield from **33**: full conversion; mp 108 °C; ^{19}F NMR −137.5 ppm. Methyl salycilate (**35**) was also reacted under these conditions in 70% conversion to give in 9% yield the *o*-fluoro isomer **36**: mp 33 °C; IR 3600, 1740 cm^{-1}; MS, m/e 170 (M^+), 139 ($M - OCH_3)^+$, 111 ($M - COOCH_3)^+$; ^{19}F NMR −137.0 ppm (d, $^3J_{HF}$ = 12.2). The known **37**[35] was obtained in 14% yield: mp 28 °C; ^{19}F NMR −124.7 ppm.

Fluorination of 38, 41, and 42 were executed by method A. In the case of **38** the usual 40–50% excess of **1** was used and the conversion was 80%. The *o*-fluoro derivative **39** was isolated in 55% yield: mp 72 °C; ^{19}F NMR −131.8 ppm. The *para* isomer was also obtained in 8% yield: ^{19}F NMR −126.7 ppm. The trifluoroacetanilide which is more deactivated was reacted with a 3-fold excess of **1**: 100% conversion. Compound **43** was obtained after chromatography on silica with 40% EtOAc as eluent in 57% yield: mp 64 °C (from CCl_4); IR 3520 and 1670 cm^{-1}; MS, m/e 207 (M^+), 138 ($M - CF_3$), 110 ($M - COCF_3$); NMR δ 8.27 (1 H at 6, m), 8.16 (1 H, NH, br s), 7.13–7.26 (4 H, m); ^{19}F NMR −130.7 (1 F, s), 76.3 (3 F, s). The pivaloylamido **42** was also fluorinated by using a 2-fold excess of **1** and 100% conversion was reached. The fluorinated compound **44** was homogenized by chromatography, using 20% EtOAc in PE, and crystallized from PE; mp 68 °C; 52% yield; IR 3440 and 1660 cm^{-1}; MS, m/e 194 (M^+), 100 ($M - COCMe_3$); NMR δ 8.33 (1 H at 6, m), 7.40 (1 H, NH, br s), 6.97–7.17 (3 H, m), 1.33 (9 H, s); ^{19}F NMR −132.7 ppm. Anal. Calcd for $C_{11}H_{14}FNO$: C, 67.7; H, 7.18. Found: C, 67.56; H, 6.95.

Fluorinations of (trifluoromethyl)acetanilides 45, 52, and 61 were all done according to method A where the acetyl hypofluorite was in 2–3-fold excess over the aromatic substrate. The reaction in the case of **45** was unusually slow and the reaction mixture was worked up only after 24 h at −78 °C. Even so the conversion was only 35%. The crude was chromatographed on HPLC, using 50% EtOAc in cyclohexane. After eluting the starting material, the pure **46** was obtained in 62% yield (based on the reacted material): mp 116 °C (from EtOH); IR 3480, 1665 cm^{-1}; MS, m/e 221 (M^+), 178 ($M - COCH_3)^+$, 152 ($M - CF_3)^+$; NMR δ 7.24–7.38 (3 H, m), 2.19 (3 H, s); ^{19}F NMR −115.8 (1 F), −61.7 ppm (3 F). Anal. Calcd for $C_9H_7F_4NO$: C, 48.87; H, 3.17. Found: C, 49.16; H. 3.38. The reaction of **52** with **1** was much faster than that of **45**, and after 10 min at −75 °C it reached a conversion of 80%. Two main products were isolated by chromatography, using 40% EtOAc in cyclohexane. The less polar compound 3-(trifluoromethyl)-6-fluoroacetanilide (**54**) was obtained in 28% yield: mp 107 °C (from MeOH); IR 3460 and 1660 cm^{-1}; MS, m/e 221 (M^+), 178 ($M - COCH_3)^+$, 152 ($M - CF_3)^+$; NMR δ 8.68 (1 H at 2, br d, $^4J_{HF}$ = 7.1 Hz), 7.53 (1 H, NH, br s), 7.16–7.33 (2 H, m), 2.25 (3 H, s); ^{19}F NMR −127 (1 F), −62.7 ppm (3 F). Anal. Calcd for $C_9H_7F_4NO$: C, 48.87; H, 3.17. Found: C, 49.1; H, 3.3. The more polar fraction 2-fluoro-3-(trifluoromethyl)acetanilide (**53**) was obtained in 34% yield: mp 98 °C (from MeOH). The main signals in IR and MS are practically the same as for **54**: NMR δ 8.48 (1 H at 6, dt, $^4J_{HF}$ = J_{HH} = 7 Hz, $^4J_{HH}$ = 2 Hz), 7.84 (1 H, NH, br s), 7.18–7.34 (2 H, m), 2.25 (3 H, s); ^{19}F NMR −133.3 (1 F), −61.8 ppm (3 F, d, $^4J_{FF}$ = 12.2 Hz). Anal. Calcd for $C_9H_7F_4NO$: C, 48.87; H, 3.17. Found: C, 48.71; 3.37. The reaction with *p*-(trifluoromethyl)acetanilide (**61**) was practically as fast as usual (couple of minutes) with practically complete conversion. The 2-fluoro-4-(trifluoromethyl)acetanilide (**64**) was homogenized by column chromatography, using CH_2Cl_2 as eluent, and crystallized from MeOH: mp 132 °C; yield 72%; IR 3460, 1660 cm^{-1}; MS, m/e 221 (M^+), 178 ($M - Ac)^+$, 152 ($M - CF_3)^+$; NMR δ 8.49 (1 H at 6, t, J_{HH} = $^4J_{HF}$ = 8.7 Hz), 7.73 (1 H, NH, br s), 7.27–7.42 (2 H, m), 2.26 (3 H, s); ^{19}F NMR −130.1 (1 F, −62.8 ppm (3 F). Anal. Calcd for $C_9H_7F_4NO$: C, 48.87; H, 3.16. Found: C, 49.08; H, 3.29.

Fluorination of 3-methylacetanilide (47) was performed according to method A with about 80–100% excess of **1** on **47** and with full conversion of the latter. The solid crude was resolved first into two fraction I and II by chromatography, using $CHCl_3$ as eluent. Each of these fractions were further chromatographed by HPLC, using 40% EtOAc in cyclohexane. The less polar compound from fraction I proved to be the 3-methyl-6-fluoroacetanilide (**49**):[36] mp 67 °C; yield 32%; IR 3400 and 1660 cm^{-1}; MS, m/e 167 (M^+), 124 ($M - COCH_3)^+$; NMR δ 8.03 (1 H at 2, br d, $^4J_{HF}$ 7.6 Hz), 7.67 (1 H, NH, br s), 7.04–6.80 (2 H, m), 2.29 (3 H, s), 2.19 (3 H, s); ^{19}F NMR −136.3 ppm. Anal. Calcd for $C_9H_{10}FNO$: C, 64.67; H, 5.95. Found: C, 64.82; H, 5.90. The more polar compound of fraction I was identified as 2-fluoro-3-methylacetanilide (**48**):[37] mp 62 °C (from MeOH); 28% yield;

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IR and MS were similar to **49**; NMR δ 8.01 (1 H at 6, m), 7.94 (1 H, NH, br s), 6.79–7.06 (2 H, m), 2.25 (3 H, d, $^4J_{HF}$ = 2.6 Hz), 2.18 (3 H, s); ^{19}F NMR −135.7 ppm. Anal. Calcd for $C_9H_{10}FNO$: C, 64.67; H, 5.99. Found: C, 64.44; H, 6.18. Fraction II was found to be a mixture of two difluoro isomers. The less polar one was 2,4-difluoro-5-methylacetanilide (**51**) in 11% yield: mp 93 °C (from MeOH); MS, *m/e* 185 (M^+), 142 ($M - COCH_3)^+$; NMR δ 8.00 (1 H at 6, t, $^4J_{HF}$ = 8.4 Hz), 7.46 (1 H, NH, br s), 6.78 (1 H at 3, t, 9.3 Hz), 2.19 (6 H, br s), ^{19}F NMR −131.5 (1 F), 119.0 ppm (1 F). Anal. Calcd for $C_9H_9F_2NO$: C, 58.38; H, 4.86. Found: C, 58.47; H, 5.14. The more polar compound isolated proved to be 2,4-difluoro-3-methylacetanilide (**50**) in 10% yield: mp 104 °C (MeOH); MS, as for **51**; NMR δ 7.97 (1 H at 6, q, J_{HH} = $^4J_{HF}$ = 8.8 Hz), 7.42 (1 H, NH, br s), 6.80 (1 H, m), 2.19 (6 H, br s); ^{19}F NMR −131.4 (1 F), −120.5 (1 F).

Fluorination of Bromoacetanilides 55 and 62. Both starting materials were reacted with **1** by method A, using a 3-fold excess of the hypofluorite. Full conversion was achieved. After the usual workup of the reaction of **55** with **1**, the crude mixture was chromatographed on HPLC, using 50% EtOAc in cyclohexane. Two fractions were isolated, and the less polar one was found to be 2-fluoro-5-bromoacetanilide (**57**): mp 113 °C (from EtOH); yield 47%; IR 3460 and 1660 cm^{-1}; MS, *m/e* 231, 233 (M^+), 188, 190 ($M^+ - COCH_3$), 152 ($M - Br)^+$; NMR δ 8.52 (1 H at 6, dd, $^4J_{HF}$ = 7 Hz, $^4J_{HH}$ = 2 Hz), 7.58 (1 H, NH, br s), 7.24–6.93 (2 H, m), 2.22 (3 H, s); ^{19}F NMR −133.0 ppm. Anal. Calcd for C_8H_7BrFNO: C, 41.38; H, 3.02. Found: C, 41.28; H, 3.06. The more polar fraction **56** had IR and MS very similar to **57**. It was obtained in 25% yield: mp 74 °C (from CCl_4); NMR δ 8.25 (1 H at 6, dt J_{HH} = $^4J_{HF}$ = 7.3 Hz, $^4J_{HH}$ = 1.5 Hz), 7.30 (1 H, NH, br s), 6.84–7.36 (2 H, m), 2.23 (3 H, s); ^{19}F NMR −125.3 ppm. When compound **62** was reacted, only one fluorine-containing product was isolated in 65% yield and it proved to be 2-fluoro-4-bromoacetanilide (**65**). The conversion in this case was rather low (about 30%) because **62** is not very soluble in $CHCl_3$ and was added as a cold suspension to **1**. **65**: NMR δ 8.22 (1 H at 6, t, J_{HH} = $^4J_{HF}$ = 7.8 Hz), 7.78 (1 H, NH, br s), 7.19–7.41 (2 H, m), 2.21 (3 H, s); ^{19}F NMR −129.1 ppm. Anal. Calcd for C_8H_7BrFNO: C, 41.38; H, 3.02. Found: C, 42.30; H, 3.60.

Fluorination of 3,5-Dimethylacetanilide (58). Method A: full conversion. The purification of the crude was achieved by chromatography. Pure 2-fluoro-3,5-dimethylacetanilide (**59**) was eluted by $CHCl_3$ and crystallized from EtOH: mp 95 °C; yield 67%; IR 3460 and 1666 cm^{-1}; MS, *m/e* 181 (M^+), 138 ($M - Ac)^+$, 123 ($M - NHAc)^+$; NMR δ 7.91 (1 H at 6, br d, $^4J_{HF}$ = 6.8 Hz), 7.37 (1 H, NH, br s), 6.70 (1 H at 4, br d, $^4J_{HF}$ = 6.8 Hz), 2.19–2.25 (9 H, m); ^{19}F NMR −141.4 ppm. Anal. Calcd for $C_{10}H_{12}FNO$: C, 66.30; H, 6.63. Found: C, 66.00; H, 6.73.

Fluorination of 4-methylacetanilide (60) was carried according to method A with a full conversion. The solid crude was chromatographed in a short silica column with chloroform as eluent and thus the known 2-fluoro-4-methylacetanilide (**63**)[38] was obtained in 85% yield: ^{19}F NMR −131.6 ppm.

Fluorination of Triphenylamine (66). Method A. Molar excess of **1** over **66** was about 5 times; full conversion. After the usual workup the crude was chromatographed on silica, using 5% EtOAc in PE as eluent. A considerable amount of polymeric and quinonic materials was absorbed on the silica, but two products still could be isolated and purified. The less polar one proved to be the trifluoro compound **67**: mp 77 °C (from EtOH); yield 28%; MS, *m/e* 299 (M^+), 204 $[(FC_6H_4)_2N]^+$, 95 $(C_6H_4F)^+$; NMR δ 7.01–7.24 (m); ^{19}F NMR −122.1 ppm. Anal. Calcd for $C_{18}H_{12}F_3N$: C, 72.24; H, 3.01; F, 19.06; N, 4.68. Found: C, 72.43; H, 4.16; F, 18.86; N, 4.98. The more polar compound **68** was obtained in 11% yield: mp 76 °C (from EtOH); MS, *m/e* 317 (M^+), 204 $[(FC_6H_4)_2N]^+$, 95 $(C_6H_4F)^+$; NMR δ 6.90–7.16 (m); ^{19}F NMR −123.5 (3 F), −119.7 ppm (1 F). Anal. Calcd for $C_{18}H_{11}F_4N$: C, 68.14; H, 3.47; F, 23.97; N, 4.42. Found: C, 68.60; H, 3.60; F, 23.10; N, 4.51.

Registry No. **1**, 78948-09-1; **2**, 321-28-8; **3**, 459-60-9; **4**, 88288-00-0; **5**, 10471-09-7; **6**, 120-57-0; **7**, 88288-01-1; **8**, 274-09-9; **9**, 88288-02-2; **10**, 151-10-0; **11**, 17715-70-7; **12**, 79069-70-8; **13**, 88288-03-3; **14**, 27602-71-7; **15**, 5263-87-6; **16**, 88288-04-4; **17**, 1078-19-9; **18**, 88288-05-5; **19**, 88288-06-6; **20**, 103-73-1; **21**, 2741-16-4; **22**, 451-80-9; **23**, 459-26-7; **24**, 91-16-7; **25**, 613-70-7; **26**, 635-67-6; **27**, 31083-15-5; **28**, 2539-21-1; **29**, 91-23-6; **30**, 484-94-6; **31**, 100-17-4; **32**, 455-93-6; **33**, 100-02-7; **34**, 403-19-0; **35**, 119-36-8; **36**, 70163-98-3; **37**, 391-92-4; **38**, 103-84-4; **39**, 399-31-5; **40**, 351-83-7; **41**, 404-24-0; **42**, 6625-74-7; **43**, 61984-68-7; **44**, 88288-07-7; **45**, 344-62-7; **46**, 88288-08-8; **47**, 537-92-8; **48**, 704-37-0; **49**, 325-74-6; **50**, 76350-71-5; **51**, 88288-09-9; **52**, 351-36-0; **53**, 88288-10-2; **54**, 349-27-9; **55**, 621-38-5; **56**, 88288-11-3; **57**, 88288-12-4; **58**, 2050-45-5; **59**, 88288-13-5; **60**, 103-89-9; **61**, 349-97-3; **62**, 103-88-8; **63**, 326-67-0; **64**, 88288-14-6; **65**, 326-66-9; **66**, 603-34-9; **67**, 88288-15-7; **68**, 88288-16-8; F_2, 7782-41-4; ^{18}F, 13981-56-1; sodium acetate, 127-09-3; benzene, 71-43-2.

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Hydrogen Cyanide Chemistry. 9. Cycloaddition Reactions and Nitrenium Ion Type Reactivity of Diiminosuccinonitrile†,[1]

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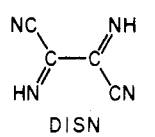
Cycloaddition reactions of diiminosuccinonitrile (DISN) with nucleophilic olefins yield a variety of products including [4 + 2] cycloadducts and aziridines. All of the products derived from 1,3-dienes, styrene, para-substituted styrenes, cycloheptatriene, norbornene, and norbornadiene can be accounted for by rearrangements of a common intermediate, zwitterionic aziridinium ion. We introduce the concept of reverse polarization and propose that DISN is a latent nitrenium ion source (isoelectronic with carbenes) and that reverse polarization of one of the >C=N bonds of DISN is responsible for the observed reactions. Comments are made on reverse polarization of other >C=X bonds, and facile 1,1-cycloreversion of aziridines is also reported.

Diiminosuccinonitrile (DISN) **1**, prepared by base-catalyzed addition of hydrogen cyanide to cyanogen, is a highly versatile polyfunctional reagent, from which a variety of heterocycles have been synthesized through condensation and displacement reactions.[2] In this paper, we focus our attention to the hetero diene unit HN=CC=NH



DISN

1

and describe its electrocyclic reactions.[1]

Because nitrogen is more electronegative than carbon,

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