Novel Process for Generating Useful Electrophiles from Common Anions Using Selectfluor® Fluorination Agent†

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In the present work, the electrophile equivalents Cl^+, Br^+, SCN^+, and NO_2^+ are generated from their respective sodium, potassium, and in some cases ammonium salts (M^+X^-) by reaction with Selectfluor electrophilic fluorination agent in acetonitrile solution at room temperature. These generated electrophilic species subsequently react in situ with a variety of aromatic substrates containing one or more substituent groups including H, F, Cl, CH_3, COOH, $C(O)CH_3$, NO_2, and OR′ and NR′R″ where R′ and R″ are H or CH_3. The resulting substitution products are, in most cases, isolable as pure compounds in high yield. Variations in the process include the use of other anions, electrophilic fluorination agents, and solvents.

Introduction

There is a general need for effective methodologies for introducing various functional groups into aromatic systems. In particular, electrophilic methodologies find widespread applications since these reactions are very well understood and the product distribution is generally predictable.[1] Despite the importance of synthetic methods for introducing electrophiles into aromatic systems, in some cases there are either relatively few reagents available to accomplish such transformations or the reagents themselves are difficult to prepare and use.

Reagents for electrophilic halogenation are available in various forms ranging from the diatomic elements to some fairly exotic halogen delivery reagents.[1−5] Most of these reagents can be prepared and isolated prior to use; however, some are available only when generated in situ. Reagents specifically useful for electrophilic halogenation include, but are not limited to, *N*-chlorosuccinimide[6−12] (NCS), *N*-chloroammonium salts,[13] *tert*-butylhypochlorite,[14] sodium chlorite/(salen)Mn(III) complex,[15] chlorine trifluoromethanesulfonate,[16] and triethylammonium trichloride[17] for chlorination; *N*-bromosuccinimide[8−12] (NBS) and alkylammonium tribromide[18] for bromination; *N*-iodosuccinimide,[19] iodine(I) triflate,[20] and dichlorohypoiodite salts[21] for iodination; and various −NF, −XeF, and −OF agents for fluorination.[6,22] In a recent report,[23] a new method for halogenation of activated aromatic substrates through the dimethyldioxirane oxidation of halide anions was disclosed.

Reagents that are known to deliver electrophilic thiocyanogen (^+SCN) include thiocyanogen,[24,25] cyanogen chloride,[26−29] and metal thiocyanates mediated by aryliodite,[30] NCS,[31,32] and NBS.[32,33]

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Scheme 1

$$F^+ + X^- \xrightarrow[\text{r.t.}]{\text{ACN}} F^- + [X^+] \qquad (1a)$$

$$ArH + [X^+] \xrightarrow[\text{r.t.}]{\text{ACN}} ArX + H^+ \qquad (1b)$$

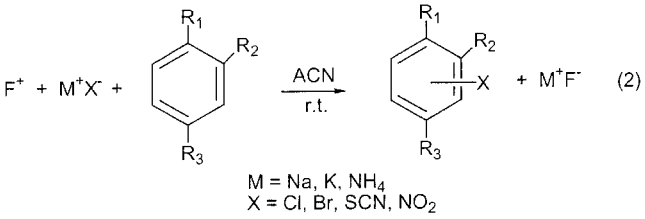
Electrophilic nitration can be accomplished using a variety of reagents, some of which include nitronium salts,[34−38] methyl nitrate,[39] and sodium nitrite mediated by trifluoroacetic acid.[40]

In the present work, we describe a new process for generating electrophiles Cl^+, Br^+, SCN^+, and NO_2^+ and have applied these in electrophilic aromatic substitution reactions of various substrates.

Results and Discussion

In the course of expanding the known reaction chemistry of Selectfluor, a commercially available and widely applicable electrophilic fluorination agent,[5,41] we discovered an interesting class of reactions that occur between various inorganic anions and a number of aromatic substrates, in the presence of Selectfluor in acetonitrile (ACN) solution. This process is depicted in general terms in Scheme 1.

We have found that the combination of Selectfluor, represented in eq 1a by F^+, and various anions, represented by X^-, in acetonitrile solvent at room temperature produces the equivalent of an X^+ electrophile such that, in the presence of an aromatic substrate (ArH), electrophilic substitution of X-for-H occurs (eq 1b). We assume that the reactions proceed via an electrophilic substitution mechanism; however, this may be an oversimplification of the actual mechanism in operation. Nevertheless, the net effect is the conversion of X^- to X^+, facilitated by the fluorine electrophile F^+, and subsequent addition of the resulting X^+ electrophile to the aromatic substrate. There is just one previous report of an electrophilic fluorination agent functioning as a mediator for effecting electrophilic reactions.[42] In this report, mixtures of anisole **2a**, Selectfluor, and I_2, KI, Me_3SiI, or MeI in solution were shown to produce iodoanisole derivatives regioselectively. This result is not surprising, however, since it had previously been established[43] that Selectfluor readily and immediately oxidizes iodide to iodine in solution.



(2)

In the present work, depicted in eq 2, the equivalents to Cl^+, Br^+, SCN^+, and NO_2^+ are generated from their respective sodium, potassium, and in some cases ammonium salts (M^+X^-) by reaction with Selectfluor in ACN or an equivalent solution, and the generated species subsequently react in situ with a variety of aromatic substrates (in eq 2, R_{1-3} can each represent a strongly deactivating to strongly activating substituent group, including H, F, Cl, CH_3, COOH, $C(O)CH_3$, NO_2, and OR′ and NR′R″ where R′ and R″ are H or CH_3) yielding the corresponding substitution products, many times in high yield and with good purity.

We have evidence also that other anions, e.g., CH_3COO^- and CF_3COO^-, are converted similarly to electrophiles for some limited examples, that other electrophilic fluorination agents and solvents also show this effect, and that electrophilic addition reactions with some nonaromatic unsaturated moieties can be effected by this reaction methodology. A discussion of the variations in this process and some process limitations is provided in the following subsections.

Reactivity of Various Anions with Aromatic Substrates. The anions that have been investigated in this general reaction process can be divided into three groups based on their observed reactivity with aromatic substrates. In the first group of anions, we found that the sodium, potassium, and in some cases ammonium salts of chloride (Cl^-), bromide (Br^-), thiocyanate (^-SCN), and nitrite (NO_2^-) are very effectively converted to their electrophile equivalents, Cl^+, Br^+, ^+SCN, and NO_2^+, respectively, in each case, and that these electrophiles readily add to a wide range of aromatic substrates.

Provided in Table 1 is a summary of experimental results for electrophilic reactions involving this primary group of anions with various aromatic substrates. Referring to Table 1, the reaction between equimolar amounts of **1a** and Br^- was ~90% complete after 3 h of reaction time, with **1b** being the major product. The reaction between **1a** and Cl^- was 42% complete after 42 h, with **1e** being the major chlorinated product (25%), but also a significant amount (67%) of **1d** was observed. In the reaction with SCN^-, just 4% of **1a** was converted after 93 h, with the *para*-thiocyanate derivative **1f** being the only product. Finally, nearly complete conversion of the **1a** was observed after 68 h in the reaction with NO_2^-, with **1g** being the predominant (81%) product.

The difference in reactivity that was observed between the anions and **1a** is representative of all the aromatic systems that were investigated and supports a general trend that has been established. That is, the reactivity of the electrophiles generated from anions with various aromatic substrates decreases in the order $Br^+ > Cl^+ > SCN^+ > NO_2^+$, with the reactions involving Br^+ being, in general, much more facile than those with NO_2^+. Thus, in the reaction involving Br^+, 90% conversion of **1a** was achieved after just 3 h, whereas with NO_2^+, 68 h was required to achieve the same conversion. The low conver-

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Table 1. Results of Experiments at Room Temperature in Acetonitrile Solvent (ACN)

aromatic, mmol	ACN (mL)	NaX, mmol	F^+[a] (mmol)	time (h)	conversion (%)	product distribution,[b,c] mol %
phenol **1a**, 10.0	80	NaBr, 15.1	9.9	3	90	bromophenol **1b**, 87; 2,4-dibromophenol **1c**, 12; fluorophenol **1d**, 1
phenol **1a**, 20.4	80	NaCl, 25.4	21.4	42	42	chlorophenol **1e**, 25; **1d**, 67; unknown, 8
phenol **1a**, 10.0	80	NaSCN, 15.1	9.9	93	4	4-SCN-phenol **1f**, 100
phenol **1a**, 10.0	80	$NaNO_2$, 14.5	9.9	68	98	nitrophenol **1g**, 81; fluoronitrophenol **1h**, 16; unknown, 3
anisole **2a**, 19.9	80	NaBr, 20.1	20.9	21	100	4-bromoanisole **2b**, 100
anisole **2a**, 21.0	80	NaCl, 22.1	20.4	42	58	chloroanisole **2c**, 67; fluoroanisole **2d**, 31; unknown, 2
anisole **2a**, 20.3	200	NaSCN, 19.7	20.0	21	67	SCN-anisole **2e**, 94; unknown, 6
anisole **2a**, 10.2	100	$NaNO_2$, 10.0	9.9	97	43	nitroanisole **2f**, 13; **2d**, 87
acetanilide **3a**, 10.0	80	NaBr, 17.0	9.9	3	87	bromoacetanilide **3b**, 99; fluoroacetanilide **3c**, 1
acetanilide **3a**, 10.0	100	NaCl, 10.3	9.9	23	53	chloroacetanilide **3d**, 73; chlorofluoroacetanilide **3e**, 5; **3c**, 22
acetanilide **3a**, 10.0	80	NaSCN, 17.3	9.9	71	0	starting material **3a** only
acetanilide **3a**, 20.1	80	$NaNO_2$, 27.0	9.9	27	10	nitroacetanilide **3f**, 95; **3c**, 5
aniline **4a**, 24.5	80	NaBr, 21.4	20.0	17	39[d]	F-aniline **4b**, 61; benzophenone **4c**, 39
aniline **4a**, 21.5	80	NaCl, 26.3	19.8	17	50[e]	**4b**, 57; **4c**, 43
aniline **4a**, 21.5	80	NaSCN, 22.4	20.0	17	82[f]	SCN-aniline **4d**, 96; **4b**, 4
aniline **4a**, 29.4	80	$NaNO_2$, 19.0	20.2	18	100[g]	**4c**, 60; unknown, 40
dimethylaniline **5a**, 9.9	80	NaBr, 9.7	9.9	42	75	bromodimethylaniline **5b**, 37; fluorodimethylaniline **5c**, 44; unknown, 19
dimethylaniline **5a**, 9.9	80	NaCl, 9.9	9.9	43	66	chlorodimethylaniline **5d**, 6; **5c**, 54; unknown, 40
dimethylaniline **5a**, 18.4	80	NaSCN, 21.3	19.8	18	98	4-SCN-dimethylaniline **5e**, 100
dimethylaniline **5a**, 9.9	80	$NaNO_2$, 10.1	9.9	68	93	nitrodimethylaniline **5f**, 38; **5c**, 43; unknown, 19
toluene[h] **6a**, 10.0	100	NaBr, 10.0	9.9	19	39	bromotoluene **6b**, 49; bromomethyltoluene **6c**, 36; unknown, 15
toluene[h] **6a**, 19.2	80	NaCl, 20.3	20.3	66	51	chlorotoluene **6d**, 100
benzene **7a**, 10.0	80	NaBr, 10.5	10.0	72	100	bromobenzene **7b**, 100
benzene **7a**, 10.0	80	NaCl, 10.1	10.0	72	100	chlorobenzene **7c**, 97; dichlorobenzene **7d**, 3
benzene **7a**, 10.0	80	NaSCN, 10.4	10.0	72	100	no SCN-benzene product, only unidentified sulfur-containing species present
benzene **7a**, 10.0	80	$NaNO_2$, 10.5	10.0	72	100	NO_2-benzene **7e**, 100
1,4-DMB **8a**, 22.3	80	NaBr, 34.7	30.0	113	100	2-bromo-1,4-dimethoxybenzene **8b**, 100
1,4-DMB **8a**, 17.9	80	NaCl, 34.8	29.7	113	100	2-chloro-1,4-dimethoxybenzene **8c**, 100
1,4-DMB **8a**, 27.6	80	NaSCN, 44.1	40.8	160	60	2-thiocyanato-1,4-dimethoxybenzene **8d**, 100
1,4-DMB **8a**, 26.1	80	$NaNO_2$, 33.5	31.0	184	100	2-nitro-1,4-dimethoxybenzene **8e**, 100
p-MAP **9a**, 10.0	80	NaBr, 10.1	10.0	95[i]	89	3′-Br-*p*-MAP[j] **9b**, 97; 2,4-dibromo-1-methoxybenzene **9c**, 2; **2b**, 1
p-MAP **9a**, 10.0	80	NaCl, 10.2	10.0	95	73	3′-chloro-*p*-MAP[j] **9d**, 97; **2c**, 3
p-MAP **9a**, 10.0	80	NaSCN, 10.1	10.0	95	47	3′-SCN-*p*-MAP[j] **9e**, 100
p-MAP **9a**, 9.9	80	$NaNO_2$, 9.8	10.0	95	≈1	**2f**, trace; 2-fluoro-4-methoxynitrobenzene **9f**, trace
p-xylene **10a**, 10.4	100	NaBr, 10.7	9.9	3	50	bromo-*p*-xylene **10b**, 78; unknown, 22
p-xylene **10a**, 23.7	80	NaCl, 33.7	21.2	162	52	chloro-*p*-xylene **10c**, 100
p-xylene **10a**, 10.4	100	NaSCN, 10.1	9.9	148	56	SCN-*p*-xylene **10d**, 82; unknown, 18
2-fluoroanisole[k] **11a**, 20.0	200	NaCl, 20.1	42.4	26	52	4-chloro-2-fluoroanisole **11b**, 96; 2,4-difluoroanisole **11c**, 2; **2c**, 2
4-fluoroanisole[k] **12a**, 20.1	200	NaCl, 20.1	42.3	26	53	2-chloro-4-fluoroanisole **12b**, 91; **11c**, 6; unknown, 3
4-nitrophenol[l] **13a**, 10.1	80	$NaNO_2$, 10.1	10.0	45	95	2,4-dinitrophenol, 100
chloro-*p*-xylene[k] **10c**, 20.0	200	NaCl, 20.0	42.4	24	58	2,5-dichloro-1,4-dimethylbenzene **10e**, 95; 2-chloro-5-fluoro-1,4-dimethylbenzene **10f**, 2; unknown, 3

[a] F^+ is Selectfluor fluorination agent, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate). [b] Product distribution is expressed as a normalized % of conversion. [c] If not specifically stated, the ortho/para isomer ratio was not determined. [d] No brominated products were found. [e] No chlorinated products were found. [f] Conversion was increased to 100% after 64 h following the addition of Selectfluor (9.8 mmol) and NaSCN (10.3 mmol). [g] No nitrated or fluorinated products were found. [h] Experiments involving **6a** and either NaSCN or $NaNO_2$ failed to show that any reaction had occurred. [i] Conversion did not change from 68 to 95 h. [j] Electrophilic aromatic substitution is presumed to occur at the 3′-position due to the directing effects of the acetyl and methoxy groups; however, this has not been established analytically. [k] Only experiments with NaCl were performed with these aromatic substrates. [l] Reactions involving **13a** and NaBr, NaCl, and NaSCN proceeded to completion; however, the products could not be unambiguously characterized.

sion (4%) observed in the reaction involving SCN^- and **1a** in ACN in the presence of Selectfluor is an unresolved anomaly to the general reactivity trend that has been established.

In the second group of anions, which includes acetate (CH_3COO^-) and trifluoroacetate (CF_3COO^-) salts, only some reactions involving these anions were successful, although conversion of the aromatic substrate was low (<5%) in each case. For instance, reactions involving equimolar amounts of Selectfluor, **10a**, and either sodium trifluoroacetate or ammonium acetate, in ACN solution at ambient temperature, produced only minor amounts of the trifluoroacyl- and acyl-substituted products, respectively.

Attempted reactions involving the third group of anions, which include cyanide (^-CN), cyanate (^-OCN), methoxide ($^-OCH_3$), and thiomethoxide ($^-SCH_3$), failed under all circumstances to show any indication of conver-

Table 2. Comparison of Reaction Rates for Chlorination of Aromatic Substrates with KCl, NaCl, and Selectfluor in ACN Solvent at Room Temperature

substrate	reaction time, h	conversion using KCl, mol %	conversion using NaCl, mol %	conversion ratio KCl/NaCl
9a	66	47[a]	44[b]	1.1
10a	90	60[c]	39[d]	1.5
6a	66	63[e]	51[f]	1.2
7a	90	13[g]	15[h]	0.9

[a] **9a** (24.3 mmol), Selectfluor (20.6 mmol), KCl (21.6 mmol) in 80 mL of ACN. [b] **9a** (20.3 mmol), Selectfluor (20.2 mmol), NaCl (26.6 mmol) in 80 mL of ACN. [c] **10a** (26.6 mmol), Selectfluor (20.0 mmol), KCl (21.1 mmol) in 80 mL of ACN. [d] **10a** (23.7 mmol), Selectfluor (21.2 mmol), NaCl (33.7 mmol) in 80 mL of ACN. [e] **6a** (21.6 mmol), Selectfluor (21.1 mmol), KCl (20.3 mmol) in 80 mL of ACN. [f] **6a** (19.2 mmol), Selectfluor (20.3 mmol), NaCl (20.3 mmol) in 80 mL of ACN. [g] **7a** (18.5 mmol), Selectfluor (20.1 mmol), KCl (20.1 mmol) in 80 mL of ACN. [h] **7a** (21.7 mmol), Selectfluor (20.2 mmol), NaCl (20.9 mmol) in 80 mL of ACN.

sion of the anion to an electrophile or of transfer of the anticipated electrophile groups "$^{+}$CN", "$^{+}$OCN", "$^{+}$OCH$_3$", and "$^{+}$SCH$_3$", respectively, to the aromatic substrate. Instead, reactions involving these anions and those aromatic substrates that are strongly activated toward electrophilic aromatic substitution, e.g., **2a**, resulted in fluorinated products being formed exclusively, e.g., **2d**. Attempted reactions involving the third group of anions and weakly activated aromatic substrates, e.g., **6a** or **10a**, failed to show any products in all cases.

Qualitative Reaction Rates of K^+ vs Na^+ for M^+Cl^- Salts. Qualitative reaction rates for the addition of Cl^+, generated from either KCl or NaCl salts, to several aromatic substrates were determined under similar conditions, and the results are summarized in Table 2. Only reactions where chlorination was observed in exclusion of fluorination are included. The rate of reaction, defined qualitatively as the % conversion of aromatic substrate achieved in a given time period, using KCl was found to be marginally faster than that for NaCl for all aromatic substrates except **7a**. The greatest difference observed was for the chlorination of **10a** where 50% more conversion was achieved in the same time period using KCl.

Aromatic Substrates Investigated. A wide range of monosubstituted aromatic substrates has been investigated in this reaction methodology, from highly activated, e.g., phenol **1a**, to nonactivated, e.g., benzene **7a**. The specific monosubstituted aromatic substrates and resulting products are depicted in Scheme 2 and summarized in Table 1. In addition, we also have found several disubstituted aromatic substrates to be active in this reaction process; the specific reactants and products are depicted in Scheme 3 and summarized in Table 1. Not all of these aromatic substrates respond the same in terms of which electrophiles will add and which will not. Moreover, the relative rate of electrophilic addition differs significantly between substrates; with some of the substrates, the reactions are sluggish, while with others, the reactions are quite facile. In general, the more activating the group on the aromatic ring toward electrophilic aromatic substitution, the more facile the reaction between the generated electrophile and the aromatic compound. Thus, using the reactions between Br^- and the aromatics for illustration, we found that **1a** is nearly fully converted to **1b** within 3 h, conversion of **2a** requires 21 h for completion, **7a** requires 72 h for complete conversion, and **9a** requires 95 h.

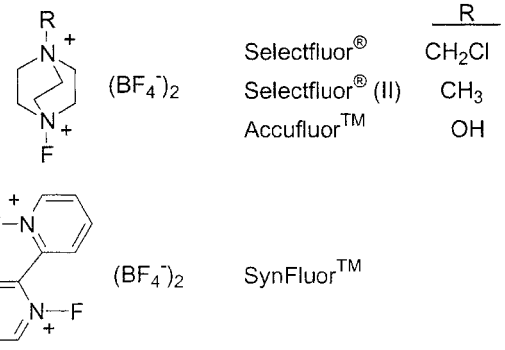
Aromatic substrates found to be unreactive in this reaction methodology include acetophenone, benzoic acid, benzonitrile, chloro- and fluorobenzene, 2-hydroxy-4-methyl-quinoline, 2-hydroxyquinoline, and nitrobenzene.

Qualitative Comparison of Reaction Rates Using Different F^+ Compounds. While a large majority of the reactions performed in the course of this work were carried out using commercial-grade Selectfluor fluorination agent, three other fluorination agents, Selectfluor (II), Accufluor, and SynFluor were also investigated in a limited subset of examples for their efficacy in this reaction methodology. The four F^+ agents used in this work are illustrated below.

Table 3. Comparison of Reaction Rates for the Chlorination of 2a and 10a in ACN Solvent with NaCl and Different Fluorination Agents[a]

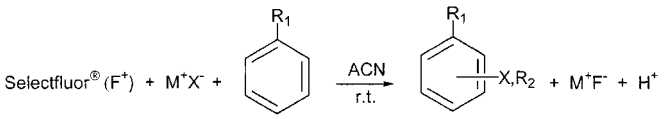
substrate	F^+ agent[b]	reaction time, h	conversion, %	product distribution (mol %)
2a	Selectfluor	117	84	**2c** (80); **2d** (20)
2a	Accufluor	117	76	**2c** (63); **2d** (37)
2a	Selectfluor (II)	115	58	**2c** (80); **2d** (20)
2a	SynFluor	163	71	**2c** (100)
10a	Selectfluor	121	74	**10c** (78); **10e** (14)
10a	Accufluor	121	54	**10c** (90); **10e** (6)
10a	Selectfluor (II)	114	42	**10c** (100)
10a	SynFluor	113	28	**10c** (100)

[a] For reactions of 10 mmol each of aromatic substrate, NaCl, and fluorination agent in 100 mL of solvent at room temperature. [b] F^+ agents are: Selectfluor, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); Selectfluor (II), 1-fluoro-4-methyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); Accufluor, 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); SynFluor, 1,1′-difluoro-2,2′-bipyridinium bis(tetrafluoroborate).



For all reactions studied in the course of this work, including those using different electrophile sources M^+X^- (M = Na, K, NH_4; X = Br, Cl, SCN, NO_2) with various aromatic substrates in different solvents, we found that Selectfluor fluorination agent affords the highest yields of substituted aromatic products in the shortest reaction time. Table 3 provides a representative comparison of the reaction rates, defined as the % conversion of aromatic

Scheme 2



Starting Materials **Aromatic Compound**, R_1 =	Products **Product Compound**	R_2 =	X =
1a R_1 = -OH	**1b**	H	Br
	1c	Br	Br
	1d	F	-
	1e	H	Cl
	1f	H	SCN
	1g	H	NO_2
	1h	F	NO_2
2a R_1 = -OCH_3	**2b**	H	Br
	2c	H	Cl
	2d	F	-
	2e	H	SCN
	2f	H	NO_2
3a R_1 = -$NHC(O)CH_3$	**3b**	H	Br
	3c	F	-
	3d	H	Cl
	3e	F	Cl
	3f	H	NO_2
4a R_1 = -NH_2 R_1 = -C(O)Ph for product **4c**	**4b**	F	-
	4c	H	-
	4d	H	SCN
5a R_1 = -NMe_2	**5b**	H	Br
	5c	F	-
	5d	H	Cl
	5e	H	SCN
	5f	H	NO_2
6a R_1 = -CH_3 R_1 = -CH_2Br for product **6c**	**6b**	H	Br
	6c	H	-
	6d	H	Cl
7a R_1 = H	**7b**	H	Br
	7c	H	Cl
	7d	Cl	Cl
	7e	H	NO_2

substrate achieved in a given time period, for chlorination of **2a** and **10a** with equimolar amounts of NaCl, aromatic substrate, and various fluorination agents, in acetonitrile solvent at ambient temperature. It is evident from the data in Table 3 that the highest conversion (of aromatic substrate) in the shortest period of time is achieved using Selectfluor, and the conversion then decreases, generally, in the order Selectfluor > Accufluor > Selectfluor (II) > SynFluor.

Qualitative Comparison of Reaction Rates Using Different Solvents. In general, we have found that ACN is the best general purpose solvent to use in this electrophilic substitution reaction methodology. We have qualitatively investigated the effect on the reaction rate of using different solvents and have found, for each of the aromatic substrates investigated in this process, that the rates of reactions with the electrophiles derived from Br^- and Cl^- are marginally faster in DMF solvent than when performed in either ACN or ACN/H_2O (50:50). On the other hand, the rates of reactions with the electrophiles derived from SCN^- and NO_2^- are considerably faster in ACN than when performed in DMF. In all cases, the rates are faster for reactions performed in ACN or DMF when compared to those carried out in propionitrile. MeOH solvent was found to be inactive in this reaction methodology. The data in Table 4 are provided as an illustration of this solvent effect and provide a qualitative comparison of the reaction rates for the chlorination of **2a** and **10a** with NaCl and Selectfluor in different solvents. It is clear from the data in Table 4 that the reaction rate for chlorination is the greatest (the highest conversion achieved in the shortest period of time) for reactions performed in DMF and decreases in the order DMF > ACN ≈ ACN/H_2O (50:50 v/v) > propionitrile.

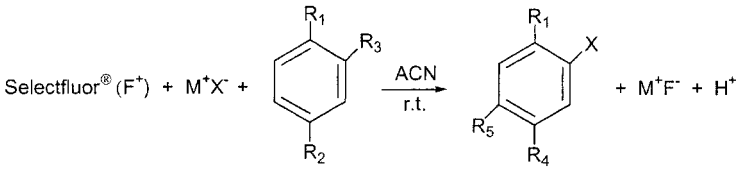
Nonaromatic Substrates Investigated. While this study focused on electrophilic reactions with aromatic substrates, a few nonaromatic compounds were investigated. For example, the reaction of equimolar amounts of NaCl, Selectfluor, and 1,3-dimethyluracil, after 94 h in ACN solvent at room temperature, did result in complete conversion of the substrate with a product distribution that included 5-chloro-1,3-dimethyluracil (24 mol %), 5-chloro-6-fluoro-1,3-dimethyluracil (41 mol %), and 5,6-dichloro-1,3-dimethyluracil (19 mol %).

Experimental Section

General. Solvents of HPLC-grade purity and other reagents were purchased commercially and used as received. Fluorination agents Selectfluor and Selectfluor (II) (Air Products and Chemicals, Inc.), Accufluor (Honeywell, Inc.), and SynFluor (SynQuest Laboratories, Inc.) are commercially available and were used as received. Unless otherwise specified, all reactions were carried out in standard glassware, under an N_2 atmosphere. Column chromatography was performed on silica gel (40−140 mesh). ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded at 300.13 and 75.47 MHz, respectively, and referenced internally to the deuterated solvent. Melting and boiling points are uncorrected. Galbraith Laboratories, Inc., Knoxville, TN, performed elemental analyses.

Characterization of Reaction Products. For all examples cited in this paper, where appropriate, characterization was performed on isolated and purified samples of the reaction products. Combinations of NMR (^1H, ^{13}C, ^{19}F), IR, and GC-

Scheme 3



Starting Materials	Products			
Aromatic Compound, $R_{1,2,3}$ =	**Product Compound**	R_4	R_5	X
8a $R_1 = R_2 = OCH_3$, $R_3 = H$	**8b**	OCH_3	H	Br
	8c	OCH_3	H	Cl
	8d	OCH_3	H	SCN
	8e	OCH_3	H	NO_2
9a $R_1 = OCH_3$, $R_2 = C(O)CH_3$, $R_3 = H$	**9b**	$C(O)CH_3$	H	Br
	9c	Br	H	Br
	9d	$C(O)CH_3$	H	Cl
	9e	$C(O)CH_3$	H	SCN
	9f	F	H	NO_2
10a $R_1 = R_2 = CH_3$, $R_3 = H$	**10b**	CH_3	H	Br
	10c	CH_3	H	Cl
	10d	CH_3	H	SCN
	10e	CH_3	Cl	Cl
	10f	CH_3	F	Cl
	10g	CH_3	F	-
11a $R_1 = OCH_3$; $R_2 = H$; $R_3 = F$	**11b** $R_1 = H$	F	OCH_3	Cl
	11c $R_1 = F$	OCH_3	F	-
12a $R_1 = OCH_3$; $R_2 = F$; $R_3 = H$	**12b**	F	H	Cl
13a $R_1 = OH$; $R_2 = NO_2$; $R_3 = H$	**13b**	NO_2	H	NO_2

Table 4. Comparison of Reaction Rates for the Chlorination of 2a and 10a with NaCl and Selectfluor in Different Solvents[a]

solvent	substrate	reaction time, h	conversion, %	product distribution (%)
DMF	**2a**	23	76	**2c** (100)
DMF	**10a**	24	31	**10c** (100)
ACN	**2a**	42	58	**2c** (67); **2d** (31); unknown (2)
ACN	**10a**[b]	18	6	**10c** (100)
		42	23	
		162	52	
ACN/H_2O 50:50 (v/v	**2a**	68	68	**2c** (25); **2d** (75)
ACN/H_2O 50:50 (v/v	**10a**	70	72	**10c** (69); **10g** (6); oxidation product (25)
propionitrile	**2a**	67	20	**2c** (60); **2d** (40)
propionitrile	**10a**	42	1	**10g** (100)
MeOH	**2a**	93	0	no reaction products
MeOH	**10a**	119	0	no reaction products

[a] For reactions of 10 mmol each of aromatic substrate, NaCl, and Selectfluor in 100 mL of solvent at room temperature. [b] Reaction was monitored by GC after 18, 42, and 162 h.

MS were employed to effect characterization. Characterization data for all reaction products were consistent with those found in the literature except for 5-acetyl-2-methoxyphenyl-1-thiocyanate **9e**, which apparently is a new composition. Characterization data for **9e** can be found later in this Experimental Section. Because of the established directing effects of the acetyl and methoxide groups in electrophilic aromatic substitution reactions,[1] compounds **9b**, **9d**, and **9e** are presumed to be the 3′-isomers as indicated in Scheme 3, and not the 2′-regioisomers, which are also possible for these compounds. There are no analytical data available that support the latter assumption.

General Procedure. In a typical experiment, Selectfluor fluorination agent (7.1 g, 20.0 mmol), NaSCN (1.6 g, 19.7 mmol), and 200 mL of ACN were combined in a 500 mL round-bottom flask containing a magnetic stir bar. Compound **2a** (2.2 g, 20.3 mmol) was added, and the contents of the flask were stirred under nitrogen and sampled periodically to monitor the reaction progress. After the mixture was stirred for 20 h at room temperature, analysis by GC and GC-MS indicated that 67% conversion of the **2a** had been achieved, with a product distribution of 1 and 62% *ortho*- and *para*-methoxyphenyl-thiocyanate **2e**, respectively. At this point, the solvent was removed in a vacuum, and the resulting residue was treated with 200 mL of deionized water. This aqueous mixture was extracted with 2 × 100 mL portions of methylene chloride; the methylene chloride extracts were combined, dried ($MgSO_4$), and then evaporated to a crude product residue. This residue was purified by chromatography on silica gel using a mixture of 5% ethyl acetate and 95% hexane. A product fraction was collected, dried over $MgSO_4$, and then analyzed by NMR, GC-MS, and GC−IR and shown to be a mixture of ortho and para isomers of **2e**, but predominately the para isomer. ^{1}H NMR ($CDCl_3$, 25 °C): δ 3.76 (s, 3H), 6.89 (d, 2H, J = 8.9 Hz), 7.44 (d, 2H, J = 8.8 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 25 °C): δ 55.26 (1C), 111.39 (1C), 113.41 (1C), 115.59 (2C), 133.49 (2C), 161.02 (1C). MS (EI) *m/e* (relative intensity): 165 (M^+, 100), 150 (74), 139(15), 122 (48), 63 (18). IR (KBr): 2173 cm^{-1}.

5-Acetyl-2-methoxyphenyl-1-thiocyanate (9e). Following the general procedure above, Selectfluor (7.2, 20.3 mmol),

9a (3.09 g, 20.6 mmol), and NaSCN (1.69 g, 20.9 mmol) were combined with 80 mL of ACN and stirred under N_2 for 96 h at room temperature. After the specified time, the solids were removed by filtration and the filtrate evaporated to near-dryness. The residue was washed with 50 mL of H_2O and extracted with 3 × 50 mL portions of methylene chloride. The organic layers were combined, dried ($MgSO_4$), and evaporated down to an orange solid. The solid was recrystallized from ethyl acetate/hexane (90/10) to afford an analytically pure sample. Yield of **9e**: 2.4 g, 11.6 mmol, 56.3%. Mp: 107−109 °C. ^{1}H NMR ($CDCl_3$, 25 °C): δ 2.56 (s, 3H), 3.98 (s, 3H), 6.97 (d, 1H, J = 8.6 Hz), 7.98 (dd, 1H, J = 8.6, 2.1 Hz), 8.14 (d, 1H, J = 2.1 Hz). ^{13}C {^{1}H} ($CDCl_3$, 25 °C): δ 26.30 (s, 1C), 56.64 (s, 1C), 109.67 (s, 1C), 110.92 (s, 1C), 113.90 (s, 1C), 130.76 (s, 1C), 131.38 (s, 1C), 131.48 (s, 1C), 159.94 (s, 1C), 195.32 (s, 1C). MS (EI) *m*/*z* (relative intensity): 207 (M^+, 35), 192 (100). Anal. Calcd for $C_{10}H_9NO_2S$: C, 57.95; H, 4.38; N, 6.76; S, 15.47. Found C, 56.86; H, 4.22; N, 6.94; S, 15.54.

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Supporting Information Available: GC-MS and ^{1}H and ^{13}C NMR spectra of compound **9e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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