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Fluorination of 4-alkyl-substituted phenols and aromatic ethers with fluoroxy and N-F reagents: Cesium fluoroxysulfate and *N*-fluoro-1,4-diazonia-bicyclo[2.2.2]octane dication salts case

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Dedicated to Prof. Dr. Boris Žemva in honor to his great contribution to fluorine chemistry.

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ABSTRACT

4-Alkyl-substituted phenols and aromatic ethers were comparatively fluorinated with electrophilic fluorinating reagents such as cesium fluoroxysulfate (CFS), *Selectfluor*™ *F-TEDA-BF*$_4$, and *Accufluor*™ *NFTh* in MeCN or MeOH. Reactions resulted in the formation of three types of products: 2-fluoro-4-alkyl-substituted corresponding compounds (**5**) as a result of *ortho* fluorination process, 4-alkyl-4-fluoro-cyclohexa-2,5-dienone compounds (**6**), resulting after an addition–elimination process, and 4-fluorosubstituted corresponding compounds (**7**) derived from *ipso* attack and release of the 4-alkyl group. The distribution of products depends on the bulkiness of alkyl groups at both positions and reaction media. The reaction in methanol proved more selective toward the formation of 2-fluoro derivatives. Tyramin and L-tyrozine were transformed with *NFTh* reagent in methanol to their fluorophenyl-substituted derivatives in good yield.

1. Introduction

The recognition that the substitution of hydrogen with fluorine can enhance the biological activity of organic compounds has been established almost 60 years ago [1]. Ever since [2–4], the fluoro-organic compounds have a profound role in medicinal materials and pharmaceuticals [5–7] and consequently in synthetic organic chemistry [8–11].

Introduction of a fluorine atom into organic compounds through an electrophilic reaction process is one of the most powerful synthetic strategies in this field of wide interest, in basic and applied research [4,8–11]. The group of compounds suitable for this type of fluorofunctionalization is known as electrophilic fluorinating reagents. In order to justify this terminology relative to reality it must be stressed that these reagents are not carriers or even a source of electrophilic fluorine since fluorine, as the most electronegative element, can hardly become F^+ specia. They have at least one common characteristic; *e.g.* the electron density flow in the first stage of electron exchange in reactions mediated by these reagents is directed from an electron rich center on a substrate toward an electron deficient center on the reagent. Besides elemental fluorine [12], the family consists of three main groups of reagents such as xenon fluorides [13], fluoroxy reagents [14], and N-F reagents [15]. These reagents indicate the type of reactive bond through which a fluorine atom is connected to the ligand part of a reagent. One of the most significant breakthroughs in modern organofluorine chemistry was accomplished during the last two decades when organic molecules incorporating a reactive N-F bond were introduced as mild fluorinating reagents with a broad synthetic application. These easily-handled "bench-top" N-F reagents, usually with optimal stability/reactivity characteristics and reasonable cost, have practically revolutionized the common perception of synthesis of fluorinated organic compounds. Manipulation of N-F reagents is an ordinary experimental protocol suitable for routine work in any organic chemistry laboratory.

Electrophilic fluorinating reagents are also strong oxidants [16] what could, due to possible competition between fluorofunctionalization and oxidation, cause a certain decrease the selectivity of their reactions, when oxidizable functional groups or heteroatoms

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are present in the target compounds. The phenolic or alkoxyaryl functional block carries a great deal of this competitive dualism. There has been a considerable interest in reactions of fluorinating reagents with phenols and aromatic ethers due to their frequent presence as a structural part of bioactive compounds. As a part of our ongoing research program focusing on the reactions of electrophilic fluorinating reagents with phenols and aromatic ethers [17–25], we now report the reactions of 4-alkyl-substituted phenols and 4-alkyl-substituted alkoxy benzene derivatives with a representative fluoroxy reagent, cesium fluoroxysulfate (CFS, **1**) and the other two popular N-F reagents from the family of *N*-fluoro-1,4-diazonia-bicyclo[2.2.2]octanedication salts, namely *Selectfluor*™ *F-TEDA-BF*$_4$ (F-TEDA-BF$_4$, **2**) and *Accufluor*™ *NFTh* (NFTh, **3**) [26].

2. Results and discussion

Steric and electronic interactions on one hand and leaving group properties on the other are the main parameters directing a course of any substitution reaction, particularly those on aromatic rings. The variation of the steric bulk of the alkyl group in *para* position and phenolic oxygen atom could influence or at least direct the regioselectivity of fluorination of 4-alkylphenols and their alkylether analogs (**4**, Scheme 1) during the reaction with a fluorinating reagent from Fig. 1.

2.1. Reactions with CFS

We started with monitoring the reaction of compounds **4** with CFS in acetonitrile as the most convenient protocol for such transformations and selected 4-methyl (**4aa**), 4-*i*-propyl- (**4ba**), 4-*t*-butylphenols (**4ca**) and the corresponding Me-, Et-, *i*-Pr, and *t*-Bu ether analogs as the suitable testing compounds. We established the formation of three types of products: 2-fluoro-4-alkyl-substituted corresponding compounds (**5**, Scheme 1) as a result of *ortho* fluorination process, similar to what has been reported for the reaction of AcOF [27], 4-alkyl-4-fluoro-cyclohexa-2,5-dienone compounds (**6**), as a result of addition–elimination process, and 4-fluoro-substituted corresponding compounds (**7**) derived from *ipso* attack and release of 4-alkyl group. As shown in Table 1, in 4-methyl series (**4aa**–**4ae**, entries 1–5), products **5** and **6** were formed and their relative ratio was considerably directed by the steric bulk of the phenolic alkyl group. The relative amount of product **5**, formed through the *ortho* attack displayed a decrease from 78% in the case of **4aa** (R^1 = H) to 29% in the case of **4ae** (R^1 = *t*-Bu) while the relative amount of addition–elimination product **6**, formed through the *para* attack, adequately increased [17]. The same effect was observed in the 4-*i*-Pr series (**4ba**–**4bd**, entries 6–9), but it was not so intensively expressed. However, in these cases the formations of fluoro-dealkylated products 7 were observed, since *i*-Pr group is a better leaving group than Me. In the *t*-Bu series (**4ca**–**4ce**, entries 10–14), 4-*t*-butylphenol gave only 2-fluoro-4-*t*-butylphenol [24]. From methoxy compound **4cb** to *i*-propoxy one **4cd,** the relative amount of 2-fluoro product decreased from 87% to 80% and fluoro-dealkylated product increased from 13% to 20%, while in the case of 4-*t*-butyl-*t*-butoxybenzene **4ce**, 65% of 2-fluoro derivative **5ce** and 35% of 4-fluoro-4-*t*-butyl-2,5-cyclohexadienone **6c** were formed. In this case,

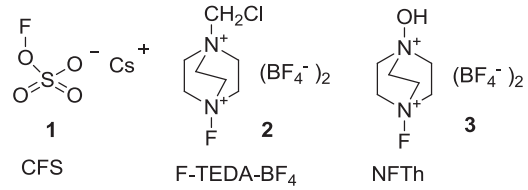
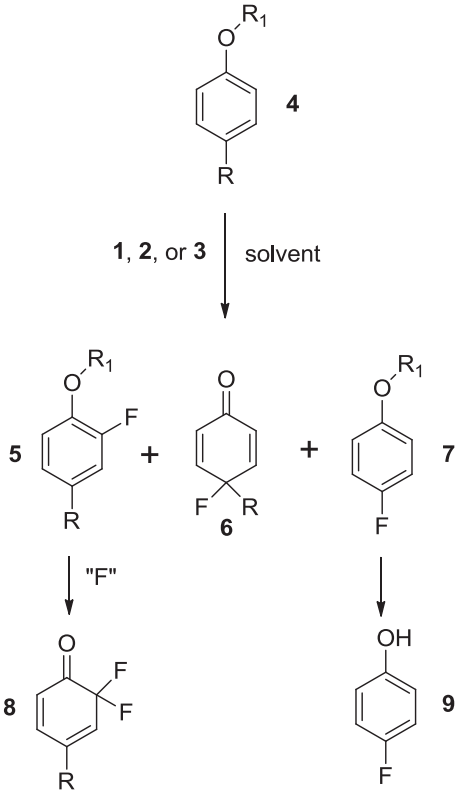
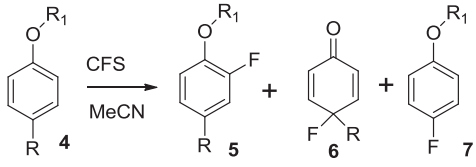


Fig. 1. Electrophilic fluorinating reagents: cesium fluoroxysulfate **1**, *Selectfluor*™ *F-TEDA-BF*$_4$ **2**, and *Accufluor*™ *NFTh* **3**.



Scheme 1. Electrophilic fluorination of 4-alkyl-substituted phenols and aromatic ethers with cesium fluoroxysulfate or N-F reagents.

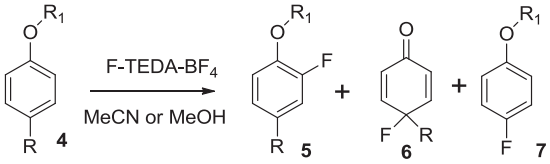
Table 1
Relative distribution of products after the reaction of 4-alkyl-substituted phenols and their ethers with CFS in MeCN.[a]



Entry	R	R^1	Relative ratio[b] (%)			Yield[c]	
			5	**6**	**7**	(%)	Ref.
1	Me	H **4aa**	78	22	–	58	[17]
2		Me **4ab**	57	43	–	64	[17]
3		Et **4ac**	52	48	–	65	[17]
4		*i*Pr **4ad**	50	50	–	64	[17]
5		*t*Bu **4ae**	29	71	–	64	[17]
6	*i*Pr	H **4ba**	80	10	10	84	
7		Me **4bb**	80	10	10	86	
8		Et **4bc**	74	13	13	86	
9		*i*Pr **4bd**	65	17	18	85	
10	*t*Bu	H **4ca**	100	–	–	83	[24]
11		Me **4cb**	87	–	13	86	
12		Et **4cc**	84	–	16	86	
13		*i*Pr **4cd**	80	–	20	86	
14		*t*Bu **4ce**	65	35	–	86	

[a] Reaction conditions: 1 mmol of **4**, 1.1 mmol CFS, MeCN (10 mL), stirred at 80 °C for 1 h.
[b] Determined from ^{19}F NMR spectra of crude reaction mixtures.
[c] Overall amount of fluorinated products determined from ^{19}F NMR spectra of crude reaction mixtures using octafluoronaphthalene (OFN) as internal standard and calculated on the starting material.

Table 2
Relative distribution of products after the reaction of 4-alkyl-substituted phenols and their ethers with F-TEDA-BF_4 in MeCN or MeOH [a]



Entry	R	R^1		MeCN			Yield[c] (%)	Ref	MeOH			Yield[c] (%)	Ref
				Relative ratio (%)[b]					Relative ratio (%)[b]				
				5	**6**	**7**			**5**	**6**	**7**		
1	Me	H	**4aa**	34	66	–	55	[23]	100	–	–	52	[23]
2		Me	**4ab**	47	53	–	60		100	–	–	50	
3		Et	**4ac**	63	37	–	60		100	–	–	55	
4		*i*Pr	**4ad**	57	43	–	58		100	–	–	58	
5		*t*Bu	**4ae**	35[d]	65	–	55		100[d]	–	–	62	
6		Bn	**4af**	40	60	–	60						
7		*m*-CF_3-Bn	**4ag**	47	53	–	55						
8		*p*-*t*Bu-Bn	**4ah**	40	60	–	60						
9	*i*Pr	H	**4ba**	40	60	–	78	[23]	62	38	–	88	[23]
10		Me	**4bb**	56	–	42	84		57	43	–	85	
11		Et	**4bc**	60	–	40	82		62	38	–	85	
12		*i*Pr	**4bd**	67	–	33	83		64	36	–	84	
13	*t*Bu	H	**4ca**	60	–	40	84	[19]	81	–	19	83	[19]
14		Me	**4cb**	80	–	20	82		90	–	10	80	
15		Et	**4cc**	68	–	32	84		79	–	21	83	
16		*i*Pr	**4cd**	68	–	32	83		80	–	20	83	
17		*t*Bu	**4ce**	62[d]	–	38[d]	70		78[d]	–	22[d]	71	

[b]Determined from ^{19}F NMR spectra of crude reaction mixtures.
[a] Reaction conditions: 1 mmol of **4**, 1.1 mmol of F-TEDA-BF_4, MeCN (10 mL), stirred at 80 °C for 1 h.
[c] Overall amount of fluorinated products determined from ^{19}F NMR spectra of crude reaction mixtures using octafluoronaphthalene (OFN) as internal standard and calculated on the starting material.
[d] Isolated only 4-substituted phenol.

two *t*-butyl leaving groups were competing, and the weaker bonded phenolic group was released from the substrate.

2.2. Reactions with F-TEDA-BF_4

The investigation was continued with a series of reactions of compounds **4** with N-F reagents **2** and **3.** The results of the course of these transformations mediated by F-TEDA-BF_4 are collected in Table 2. In the 4-methyl series of compounds, (entries 1–8), similarly as in CFS case, the reactions in MeCN afforded only products **5** and **6**. The trend of regioselectivity was found to be opposite, since increasing of the steric bulk of phenolic alkyl group increased the relative amount of 2-fluoro product **5** and decreased the amount of 4-fluoro adduct **6**. Steric hindrance is obviously not a dominant factor regulating the course of this reaction. In the case of 4-methyl-*t*-butoxybenzene (**4ae**, entry 5), the same class of products has formed albeit with a reversed distribution when compared with the fluorination of 4-methyl phenol **4aa**. Under the reaction conditions, *t*-butoxy compound **4ae** rapidly hydrolyzed to phenol **4aa**. The cleavage of phenolic alkyl groups was significant and in order to trap them we prepared the benzyl ether derivatives **4af**–**4ah**. In crude reaction mixtures, following the reaction with F-TEDA-BF_4 in MeCN we detected and subsequently isolated the corresponding benzylacetamides $AcNHR^1$ (**10**) as a result of Ritter type trapping of released carbocation $^+R^1$ with MeCN. In addition, we have further studied the effect of solvent on the course of reactions of compounds **4aa**–**4ae** with F-TEDA-BF_4 reagent. To our delight, we have established that 2-fluoro derivatives **5aa**–**5ad** were formed regiospecifically in methanol.

In the 4-*i*Pr-substituted series (**4ba**–**4bd**, entries 9–12 Table 2), the reaction in MeCN afforded 2-fluoro-substituted derivatives **5ba**–**5bd** and 4-fluoro dealkylated derivatives **7a**–**d**, except in the case with phenol **4ba** where **5ba** and **6b** were formed in 2/3 relative ratio. Furthermore the relative amount of 2-fluoro products increases with the increased bulkiness of R^1 substituent. In methanol, the reactions resulted in the formation of 2-fluoro-substituted and 4-fluoro-addition-elimination products in approximately 3/2 relative ratio, independently of the choice of R^1 substituent.

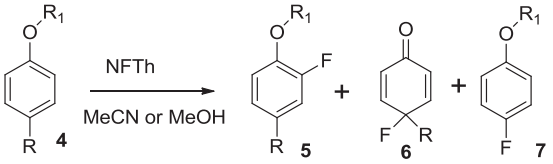
Reactions of 4-*t*Bu-substituted compounds **4** (**4ca**–**4ce**, entries 13–17, Table 2) with F-TEDA-BF_4 in MeCN as well as in MeOH resulted in the formation of 2-fluoro-substituted and 4-fluoro-dealkylated products. Interestingly, the regioselectivity of reactions carried out in MeOH was significantly higher thus favoring the formation of the 2-fluoro-substituted products.

2.3. Reactions with NFTh

Relative distribution of products after the reactions of compounds **4** with NFTh in MeCN or MeOH is shown in Table 3. General trend of this set of results is comparable to those obtained after the analogous reactions with F-TEDA-BF_4. It is worthy to mention that NFTh have mediated the reactions more regioselectively than F-TEDA-BF_4. In cases where 4-Me- and 4-*i*-Pr-substituted compounds in MeCN and 4-*t*-Bu-substituted compounds in MeOH were fluorinated with NFTh, comparatively a higher degree of the formation of 2-fluoro functionalized products was observed.

We have already demonstrated that during the reactions of 4-alkyl-substituted phenols (R^1 = H) with N-F reagents, the reaction temperature strongly influenced the distribution of products. By increasing the reaction temperature, the relative amount of fluoro-dealkylated products **7** increased the amount of addition–elimination products **6** decreased for the same degree while the

Table 3
Relative distribution of products after the reaction of 4-alkyl-substituted phenols and their ethers with NFTh in MeCN or MeOH [a]



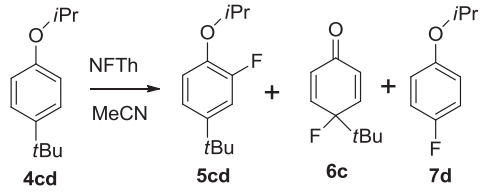
Entry	R	R^1	MeCN				Yield[c] (%)	Ref.	MeOH			Yield[c] (%)	Ref.
				Relative ratio[b] (%)					Relative ratio[b] (%)				
				5	**6**	**7**			**5**	**6**	**7**		
1	Me	H	**4aa**	41	59	–	53	[23]	100	–	–	60	[23]
2		Me	**4ab**	57	43	–	51		100	–	–	54	
3		Et	**4ac**	67	33	–	51		100	–	–	61	
4		*i*Pr	**4ad**	68	32	–	56		100	–	–	58	
5		*t*Bu	**4ae**	40[d]	60	–	48		100[d]	–	–	46	
6	*i*Pr	H	**4ba**	47	53	–	87	[23]	67	33	–	88	[23]
7		Me	**4bb**	75	–	25	83		61	39	–	84	
8		Et	**4bc**	74	–	26	86		64	36	–	85	
9		*i*Pr	**4bd**	89	–	11	85		76	24	–	86	
10	*t*Bu	H	**4ca**	61	–	39	92	[23]	90	–	10	91	[23]
11		Me	**4cb**	61	–	39	88		83	–	17	90	
12		Et	**4cc**	66	–	34	91		80	–	20	89	
13		*i*Pr	**4cd**	69	–	31	91		87	–	13	88	
14		*t*Bu	**4ce**	59[d]	–	41[d]	78		90[d]	–	10[d]	80	

[a] Reaction conditions: 1 mmol of **4**, 1.1 mmol of NFTh, MeCN (10 mL), stirred at 80 °C for 1 h.
[b] Determined from ^{19}F NMR spectra of crude reaction mixtures.
[c] Overall amount of fluorinated products determined from ^{19}F NMR spectra of crude reaction mixtures using octafluoronaphthalene (OFN) as internal standard and calculated on the starting material.
[d] Isolated only 4-substituted phenol.

relative amount of 2-fluoro-substituted products **5** remained constant [23]. The data collected in Table 4 reveals that in the case of phenol ether analogs the reaction temperature has no effect on the distribution of products, at least when 4-*t*-butyl-*i*-propoxy benzene **4cd** is used as the target compound since in the temperature range from 15 °C to 80 °C distribution of products remains constant.

In order to benefit from the results of this investigation, we decided to fluorinate some bioactive compounds bearing 4-alkyl-substituted phenol ring. Tyramine and tyrozine match closely to target candidates. Since free amino functionality hardly survives in the presence of electrophilic fluorinating reagents [8,12–15,26], its protection by acetylation was necessary in both molecules, as well as esterification of L-tyrozine carboxylic group of 4-(2-*N*-ecetylaminoethyl)-phenol (*N*-acetyl tyramin, **11a**, Scheme 2) and methyl 2-acetamido-3-(4-hydroxyphenyl) propanoate (L-*N*-acetyl tyrosine methyl ester, **11b**) were treated with NFTh in MeOH under reflux for 18 h. Purification of crude reaction mixtures using preparative TLC afforded 2-fluoro-substituted derivatives **12** in nearly 60% yield.

Table 4
Effect of temperature on the relative distribution of products after the reaction of 4-*t*-butyl-*i*-propoxybenzene **4cd** with NFTh in MeCN [a]

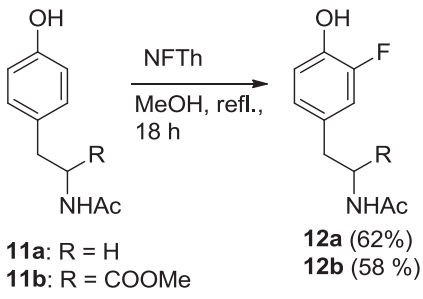


Entry	*T* (°C)	Time (h)	Relative ratio[b] (%)			Yield[c] (%)
			5cd	**6c**	**7d**	
1	15	24	69	–	31	88
2	20	20	69	–	31	89
3	25	16	69	–	31	90
4	35	12	69	–	31	90
5	50	4	69	–	31	91

[a] Reaction conditions: 1 mmol of **4cd**, 1.1 mmol NFTh, MeCN (10 mL), stirred at 15–50 °C for 4–24 h.
[b] Determined from ^{19}F NMR spectra of crude reaction mixtures.
[c] Overall amount of fluorinated products determined from ^{19}F NMR spectra of crude reaction mixtures using octafluoronaphthalene (OFN) as internal standard and calculated on the starting material.

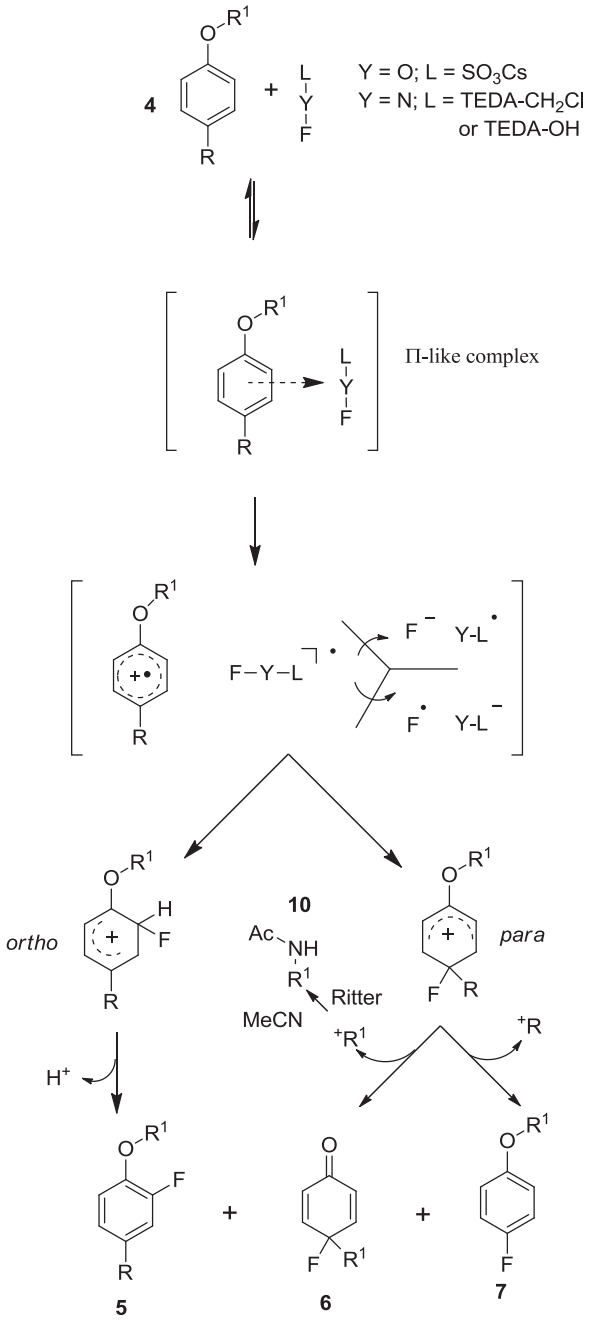
2.4. Mechanistic discussion

Concerning the possible reaction mechanism of electrophilic fluorinating reagents with organic compounds, two concepts are under discussion and dispute. The main topic of discussion is whether the reactions proceeds following the direct fluorine transfer, or through the two-step single electron transfer (SET) [28]. Direct fluorine transfer is considered as a classical S_N2 process on fluorine attacked by an electron-rich center of an organic molecule resulting in displacement of the ligand part of the reagent, which should be a better leaving group than fluoride. The



Scheme 2. Fluorination of *N*-acethyl tyramine and L-*N*-acetyl tyrozine methyl ester.

SET concept anticipates the initial formation of a charge-transfer complex (II-like) between an electron-rich organic molecule and electron deficient fluorinating reagent which after one-electron transfer transforms to organic molecule cation radical intermediate as the precursor of fluorinated or non-fluorinated products and reagent radical, a source of very reactive fluorine carrying species such as F•, F− or F-Y-L•. The formation of cation radicals has been confirmed by ESR and UV spectroscopy in the case of halogenation of activated aromatics with N-halogen reagents such as N-bromo- and N-chlorosuccinimide [29]. Since N-F or fluoroxy reagents are even stronger oxidants [16], the SET reaction pathway of the reactions with organic molecules is very plausible. However, it was generally accepted that the course of these reactions is strongly dependent on the structure of electrophilic fluorinating reagent, the structure of the target organic molecule and the reaction conditions [30–33]. Hence, it is very difficult to define unequivocally the reaction channel through which the products are formed.



Scheme 3. The reaction pathway of the fluorination of 4-alkyl-substituted phenols an aromatic ethers with cesium fluoroxysulfate or N-F reagents.

According to the results obtained in this study and those reported and discussed in some of our previous papers on similar matter [22,23,25], we believe that the reaction pathway illustrated in Scheme 3 is the most probable one. The initial interaction between electron-rich aromatic compound **4** and electron-deficient F-Y-L reagent resulted in the formation of substrate-reagent charge-transfer complex, which after one-electron transfer transforms into the aromatic molecule cation radical active intermediate and fluorine containing active species which each of them could attack cation radical at *ortho* or *para* position resulting, following already discussed processes [22], in the formation of *ortho*-fluoro and *para*-fluoro aryl cations. Elimination of proton from *ortho*-fluoro cation intermediate gives 2-fluoro-substituted products **5**, while *para*-fluoro cation could release an alkyl cation from a phenolic oxygen thus resulting in the formation of 4-alkyl-4-fluoro-cyclohexa-2,5-dienone compounds (**6**). Releasing the alkyl carbocation from *para* position gives 4-fluoro-substituted products **7**. As already mentioned in the present work and in some our previous reports [25,34], we succeeded in Ritter-type trapping of stable-enough benzyl carbocations bonded to phenolic oxygen, while carbocations released from the *para* position probably had too short of a lifetime to be trapped in the same manner. However, it has been suggested that aromatization of 4-*t*-butyl-4-fluoro-2,5-cyclohexa-2,5-dienone (**6c**) to 4-fluoro phenol (**7a**) proceeds through isobutene release [35]. In the case of phenols, we established that 4-fluoro phenol was formed after aromatization of corresponding cylohexadienone products **6a–c** under the reaction conditions using N-F reagents **2** or **3** [23]. Additionally in the case of fluorination of 4-alkyl-substituted phenylethers, products **6** and **7** were directly formed from the *para*-fluoro carbocations as proved by data collected in Table 4.

3. Conclusions

In summarizing the observations given in Tables 1–4 the following claims could be given:

(a) Concerning the effects of alkyl groups R to the distribution of products **5–7**, by increasing the bulkiness of R bonded to the position 4, the relative amount of 2-fluoro functionalization increased, while due to an extensive branching, 4-fluoro-dealkylated products **7** prevailed over 4-fluoro-addition–elimination **6** ones. Steric hindrance and better leaving group ability effected the distribution of products, which was observed in the reactions with all three reagents.

(b) The steric bulk of phenolic alkyl group R^1 regulates the distribution of *ortho*/*para* products (**5**/**6**+**7**) only in the case of reactions with CFS, while in the case of F-TEDA-BF_4 or NFTh mediation, the trend is opposite. This could be explained by prevailed electronic effects over steric hindrance in the regulation of the reaction course.

(c) The reactions of substrate **2** or **3** in MeOH leading toward the formation of 2-fluoro-substituted products are more regioselective then reactions performed in MeCN. Under the same reaction conditions, NFTh reagent was often found to be more selective than F-TEDA-BF_4.

4. Experimental

4.1. General

Melting points were determined on a Büchi 535 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM 360L at 60 MHz or on a Varian INOVA 300 spectrometer at 300 MHz, and

^{13}C NMR spectra on the same instrument at 76 MHz. Chemical shifts are reported in parts per million using TMS as internal standard. ^{19}F NMR spectra were recorded on Varian EM 360L at 56.4 MHz or on Varian INOVA 300 at 285 MHz and chemical shifts are reported in parts per million using CCl_3F as internal standard. IR spectra were recorded on Perkin-Elmer 1310 spectrometer. Standard KBr pellet procedures were used to obtain IR spectra of solids, while a film neat material was used to obtain IR spectra of liquid products. Mass spectra were obtained an Autospec Q instrument under electron impact (EI) conditions at 70 eV or under ESI conditions. Elemental analyses were carried on a Perkin-Elmer 2400 CHN analyzer.

Cesium fluoroxysulfate was prepared according to literature [36], *Selectfluor*™ *F-TEDA-BF*$_4$ (Appolo) was used as purchased, while *Accufluor*™ *NFTh* (AlliedSignal, 50% w/w on Al_2O_3) was crystallized from an MeCN/MeOH mixture in order to remove alumina, dried *in vacuo* at 20 °C and used. 4-Alkyl-substituted phenols were obtained from commercial sources, while 4-alkylphenyl alkyl ethers **4** were prepared from alkyl halogenides and corresponding 4-alkyl-substituted sodium phenolates following Williams's procedure [37]. Data for thus obtained compounds **4** were in agreement with data from literature while the new compound **4ag** was identified according to spectroscopic data.

4.2. 4-Methylphenyl 3-trifluoromethylbenzyl ether (4ag)

White crystals (from petroleum ether); mp 50.5–51.0 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H), 5.06 (s, 2H), 6.87 (d, J = 9.0 Hz, 2H), 7.45–7.7 (m, 6H); ^{19}F NMR (56.4 MHz, CCl_4): δ-64.24 (s); MS (EI, 70 eV): m/z 266 (M^+, 44%), 159 (100), 109 (20), 77 (15); IR (KBr): ν(cm^{-1}) 2950, 2890, 2850, 1890, 1610, 1585, 1515, 1455, 1340, 1330, 1245, 1190, 1165, 1130, 1050, 925, 815, 800, 770, 740, 700, 665; analysis calcd. for $C_{15}H_{13}F_3O$: C 67.66%, H 4.92%; found: C 67.81, H 4.74.

4.3. Fluorination of 4-alkyl-substituted phenols and aromatic ethers with CFS (1), Selectfluor™ F-TEDA-BF$_4$ (2) or Accufluor™ NFTh (3); general procedure

To a solution of substrate **4** (1 mmol) in 10 mL of solvent (MeCN or MeOH) was added reagents **1**, **2**, or **3** (1.1 mmol). The reaction mixture was further-stirred under reflux for 2 h. The solvent was distilled off under reduced pressure. The crude reaction mixture was dissolved in 50 mL of CH_2Cl_2, insoluble reaction products filtered off, filtrate washed with water (30 mL), the organic layer dried over Na_2SO_4, and solvent evaporated. The crude reaction mixture was analyzed by ^1H and ^{19}F NMR spectroscopy. Relative distribution of fluorinated products and their overall yield was determined from ^{19}F NMR of crude reaction mixtures using octafluoronaphthalene (OFN) as internal standard. Products were identified by comparison of their NMR spectroscopic data with those known from literature, independently prepared products or they were transformed to known compounds. 2-Fluoro-4-alkyl substituted phenols or alkoxy benzenes (**5**, Scheme 1) were thus transformed with an excess of reagents [19,20,24] to 2,2-difluoro-4-alkyl-3,5-cyclohexadienones (unknown compounds **8b** or **8c** [19]) or hydrolyzed [38] to 2-fluoro-4-methylphenol (**4aa**) [39]. 4-Fluoro-4-alkyl-2,5-cyclohexadienones **6a** [40], **6b** [21], and **6c** [23] were isolated from crude mixtures using preparative TLC (SiO_2, CH_2Cl_2/petroleum ether 4/1) and identified according to their spectroscopic data, while 4-fluoro alkoxy benzene derivatives were hydrolyzed to 4-fluorophenol (**9**) or compared to independently prepared compounds [36].

4.4. 2,2-Difluoro-4-i-propylcyclhexa-3,5-dienone (8b)

The reaction of 1 mmol (178 mg) of 4-*i*-propyl-*i*-propoxybenzene (**4bd**) with 2.2 mmol of *Accufluor*™ *NFTh* in MeCN gave 165 mg of crude reaction mixture. Purification by column chromatography (SiO_2, elution with EtOAc) afforded 115 mg (66.8%) of **8b** as white crystals; mp 38.0–40.0 °C; ^1H NMR (60 MHz, CCl_4): δ 1.1 (d, J = 9.1 Hz, 6H), 2.5 (m, 1H), 5.92–6.33 (m, 2H), 7.02 (d, J = 15.0 Hz, 1H); ^{19}F NMR (56.4 MHz, CCl_4): δ-105.03 (m); MS (EI, 70 eV): m/z 172 (M^+, 90%), 157 (100), 152 (53), 129 (50), 91 (26), 69 (93); HRMS: calcd. for $C_9H_{10}F_2O$ m/z: 172.0700, measured m/z 172.0696; IR (KBr): ν 1690 cm^{-1}; analysis calcd. for $C_9H_{10}F_2O$: C 62.78%, H 5.85%; found: C 62.82, H 5.95.

4.5. 2,2-Difluoro-4-t-butylcyclhexa-3,5-dienone [19] (8c)

The reaction of 1 mmol (192 mg) of 4-*t*-butyl-*i*-propoxybenzene (**4cd**) with 2.2 mmol of *Accufluor*™ *NFTh* in MeOH gave 150 mg of crude reaction mixture. Purification by column chromatography (SiO_2, elution with EtOAc) afforded 118 mg (63.4%) of **8c** as white crystals; mp 53.4–55.2 °C; ^1H NMR (60 MHz, CCl_4): δ 1.22 (s, 9H), 6.02–6.22 (m, 2H), 7.2 (d, J = 12.0 Hz, 1H); ^{19}F NMR (56.4 MHz, CCl_4): δ-103.03 (d, J = 6.5 Hz); IR (KBr): ν 1695 cm^{-1}.

4.6. 4-Fluoro-4-methylcyclohexa-2,5-dienone [40] (6a)

The reaction of 1 mmol (108 mg) of 4-methylphenol (**4aa**) with 1.1 mmol of *Selectfluor*™ *F-TEDA-BF*$_4$ in MeCN gave 110 mg of crude reaction mixture. Separation by preparative TLC (SiO_2, CH_2Cl_2/petroleum ether 4/1) afforded 41 mg of (31.7%) of **6a** as liquid; ^1H NMR (60 MHz, CCl_4): δ 1.42 (d, J = 22.1 Hz, 3H), 6.1 (d, J = 9.2 Hz, 2H), 6.8 (dd, J = 9.2 Hz, 6.2 Hz, 2H); ^{19}F NMR (56.4 MHz, CCl_4): δ-147.52 (qt, J = 12.1 Hz, 6.2 Hz); IR (neat): ν: 1670 cm^{-1}.

4.7. 4-Fluoro-4-i-propylcyclohexa-2,5-dienone [21] (6b)

The reaction of 1 mmol (136 mg) of 4-*i*-propylphenol (**4ba**) with 1.1 mmol of *Selectfluor*™ *F-TEDA-BF*$_4$ in MeCN gave 125 mg of crude reaction mixture. Separation by preparative TLC (SiO_2, CH_2Cl_2/petroleum ether 4/1) afforded 64 mg of (42%) of **6b** as liquid; ^1H NMR (60 MHz, CCl_4): δ 1.05 (d, J = 9.1 Hz, 6H), 2.13 (m, 1H), 6.2 (d, J = 12.3 Hz, 2H), 6.95 (dd, J = 12.3 Hz, 9.1 Hz, 2H); ^{19}F NMR (56.4 MHz, CCl_4): δ-153.32 (m); MS (EI, 70 eV): m/z 154 (M^+, 31%), 139 (100), 112 (80), 109 (17), 91 (27) IR (neat): ν: 1670 cm^{-1}.

4.8. 4-Fluoro-4-t-butylcyclohexa-2,5-dienone [23] (6c)

The reaction of 1 mmol (206 mg) of 4-*t*-butyl-*t*-butoxybenzene (**4ce**) with 1.1 mmol of CFS in MeCN gave 175 mg of crude reaction mixture. Separation by preparative TLC (SiO_2, CH_2Cl_2/petroleum ether 4/1) afforded 49 mg of (29%) of **6c** as yellow crystals; mp 63.3–63.5 °C; ^1H NMR (60 MHz, CCl_4): δ 1.12 (d, J = 19.2 Hz, 9H), 6.3 (d, J = 13.1 Hz, 2H), 7.0 (dd, J = 17.1 Hz, 13 Hz, 2H); ^{19}F NMR (56.4 MHz, CCl_4): δ-165.33 (m); MS (EI, 70 eV): m/z 168 (M^+, 21%), 153 (75), 135 (65), 125 (35), 109 (17), 91 (12), 57 (100) IR (neat): ν: 1675 cm^{-1}.

4.9. N-(3-fluoro-4-hydroxyphenethyl)acetamide (12a)

The reaction of 1 mmol (180 mg) of *N*-acetyl tyramin (**11a**) with 1.1 mmol of *Accufluor*™ *NFTH* in MeOH gave 170 mg of crude reaction mixture. Separation by preparative TLC (SiO_2, CH_2Cl_2) afforded 122.5 mg (62%) of **12a** as white crystals; mp 113.2–114.3 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 1.98 (s, 3H), 2.71 (t, J = 6.9 Hz, 2H), 3.22 (m, 2H), 6.00 (bs, 1H), 6.72–7.03 (m, 3H), 8.40 (bs, 1H); ^{13}C NMR (76 MHz, $CDCl_3$): δ 23.5, 34.5, 41.0, 116.0 (d, J = 18.1 Hz), 117.9 (d, J = 3.0 Hz), 124.5 (d, J = 3.2 Hz), 130.7 (d, J = 5.7 Hz), 143.2 (d, J = 13.0 Hz), 151.5 (d, J = 240.8 Hz), 170.2; ^{19}F NMR (285 MHz, $CDCl_3$): δ- 137.8 (dd, J = 11.7 Hz, 9.1 Hz); MS (ESI):

m/*z* 198.1 (M+H); HRMS calcd. for $C_{10}H_{12}FNO_2$: *m*/*z* 198.0930; measured: *m*/*z* 198.0933.

4.10. Methyl 2-acetamido-3-(3-fluoro-4-hydroxyphenyl)propanoate (12b)

The reaction of 1 mmol (238 mg) of L-*N*-acetyl tyrosine methyl ester (**11b**) with 1.1 mmol of *Accufluor*™ *NFTH* in MeOH gave 215 mg of crude reaction mixture. Separation by preparative TLC (SiO_2, CH_2Cl_2) afforded 148 mg (58%) of **12b** as white crystals; mp 129.0–129.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.03 (s, 3H), 3.0 (dd, *J* = 14.1 Hz, 5.8 Hz, 1H), 3.1 (dd, *J* = 14.1 Hz, 5.8 Hz, 1H), 3.81 (s, 3H), 4.81 (m, 1H), 5.92 (bs, 1H), 6.03 (bs, 1H), 6.62–7.02 (m, 3H); ^{13}C NMR (76 MHz, $CDCl_3$): δ 23.14, 37.13, 52.53, 53.21, 116.21 (d, *J* = 18.2 Hz), 117.42 (d, *J* = 2.3 Hz), 125.63 (d, *J* = 3.4 Hz), 128.43 (d, *J* = 5.8 Hz), 142.92 (d, *J* = 13.9 Hz), 150.81 (d, *J* = 238.4 Hz), 169.92, 172.03; ^{19}F NMR (285 MHz, $CDCl_3$): δ- 137.83 (dd, *J* = 11.7 Hz, 9.1 Hz); ^{19}F NMR (285 MHz, $CDCl_3$): δ- 140.43 (dd, *J* = 9.9 Hz, 9.2 Hz); MS (ESI): *m*/*z* 256.1 (M+H); HRMS calcd. for $C_{12}H_{15}FNO_4$: *m*/*z* 256.0985; measured: *m*/*z* 256.0991.

4.11. Isolation of acetamides as side products in fluorination of 4-alkyl-substituted aromatic ethers

In the case of reactions of 4-methylphenyl 3-trifluoromethylbenzyl ether (**4ag**) or 4-methylphenyl 4-*t*-butylbenzyl ether [41] (**4ah**) with *Selectfluor*™ *F-TEDA-BF*$_4$ in MeCN (see Table 2) we isolated using preparative TLC (SiO_2; CH_2Cl_2/EtOH 95/5) the following side products: **N-(3-trifluoromethyl)benzylacetamide** [42] (**10g**): mp 55.5–56.8 °C (mp [42] 56–57 °C); ^{1}H NMR (60 MHz, $CDCl_3$): δ 2.12 (s, 3H), 4.53 (m, 2H), 7.33 (m, 1H), 7.42–7.82 (m, 4H); ^{19}F NMR (56.4 MHz, CCl_4): δ-64.52 (s); MS (EI, 70 eV): *m*/*z* 217 (M^+, 60%), 174 (45), 135 (65), 159 (100), 149 (65), 69 (52); or **N-(4-t-butyl)benzylacetamide** [43] (**10h**) mp 74.5–76.8 °C (mp [43] 75–78 °C); ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.32 (s, 9H), 2.0 (s, 3H), 4.42 (d, *J* = 6.1 Hz, 2H), 6.03 (brs, 1H), 7.23–7.43 (m, 4H); MS (EI, 70 eV): *m*/*z* 205 (M^+, 75%), 190 (100), 162 (15), 149 (20), 148 (80), 132 (32), 131 (65), 106 (91); HRMS calcd. for $C_{13}H_{19}NO$ *m*/*z*: 205.1436, measured *m*/*z* 205.1467.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2013.07.002.

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