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Fluorination of Aromatic Compounds with *N*-Fluorobenzenesulfonimide under Solvent-Free Conditions

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Abstract—Reactions of *N*-fluorobenzenesulfonimide with methylbenzenes, phenols, and phenol ethers were studied under solvent-free conditions. The rate constant ratio for the reactions with mesitylene and durene indicates polar mechanism of the process. Solvent-free fluorination of aromatic compounds with *N*-fluorobenzenesulfonimide in some cases is more selective than reactions with other N–F reagents in a solvent.

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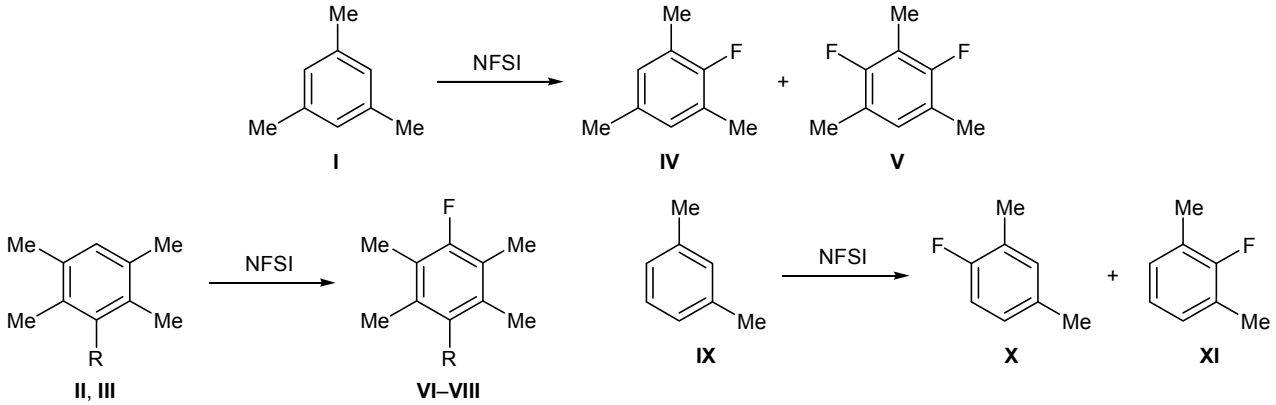
Fluorinated aromatic compounds are widely used as pesticides, medicinal agents, and various functional materials; therefore, development of ecologically friendly and selective fluorination procedures seems to be an important problem [1–3]. During the past two decades, N–F reagents [1–17] have been extensively used as source of fluorine in mild and selective fluorination of organic compounds. In particular, such reagent is *N*-fluorobenzenesulfonimide (NFSI) [2, 4, 7–9, 18–24]. It is nonhygroscopic, stable to storage, and convenient to handle with. *N*-Fluorobenzenesulfonimide is quite reactive, but at the same time it exhibits a moderate oxidative ability [2], which is important for fluorination of organic compounds with low oxidation potentials. *N*-Fluorobenzenesulfonimide is commonly used to effect fluorination of carbanions, enolates, and enol ethers in the synthesis of fluorinated intermediate products necessary for the manufacture of medicinal agents [7–9]. Direct fluorination of aromatic compounds with NFSI was performed less frequently than with other N–F reagents, e.g., 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts [1–24].

The goal of the present work was to study the selectivity in fluorination of aromatic compounds, namely methyl-substituted benzenes, phenols, and phenol ethers, with NFSI in the absence of a solvent. The selectivity problem in electrophilic fluorination under these conditions remains poorly studied (cf. [22]).

We have found that the yield of monofluoro derivatives in the fluorination of polymethylbenzenes

Scheme 1.



II, **VI**, R = H; **III**, **VIII**, R = Me; **VII**, R = F.

Table 1. Fluorination of methyl-substituted benzenes, phenols, and phenol ethers with *N*-fluorobenzenesulfonimide under solvent-free conditions[a]

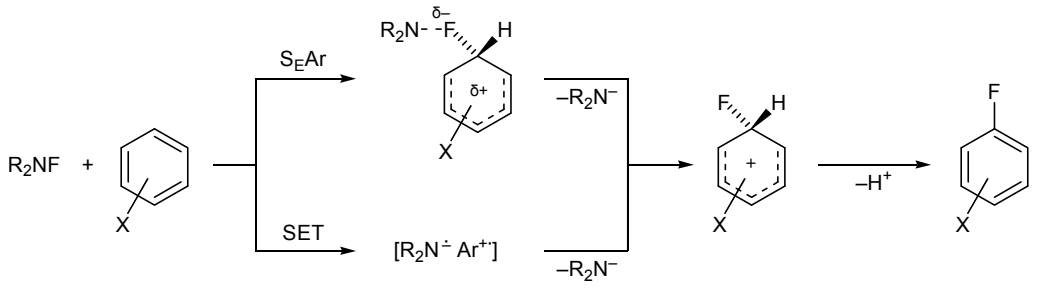
Compound no.	Temperature, °C	Time, h	Product (fraction, %)	Overall yield, %
I	105	1.67	**IV** (97), **V** (3)	65
II	105	1.67	**VI** (98), **VII** (2)	13
III	105	1.67	**VIII**	10
IX	105	1.67	**X** (59), **XI** (41)	6
IX	105	22	**X** (62), **XI** (38)	52
XX	105	0.5	**XXIII**	24
XXI	105	3	**XXIV**	30
XXII	105	3	**XXV**	7
XXVI	105	0.5	**XXVII** (92), **XXVIII** (4), **XXIX** (4)	66
XXX	105	0.33	**XXXI**	75
XXXIII	90	3	**XXXIV** (70), **XXXV** (30)	61

[mesitylene (**I**), durene (**II**), and pentamethylbenzene (**III**)] with NFSI under solvent-free conditions decreases as the number of methyl groups in the aromatic ring increases (Scheme 1, Table 1). A probable reason is *ipso*-attack by the reagent, which promotes side reactions (cf. [25]).

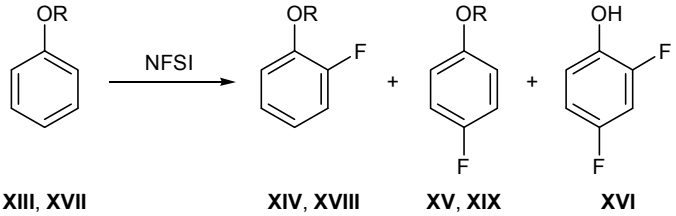
The reactions of NFSI with mesitylene and durene afforded mainly only one product, whereas fluorination of *m*-xylene (**IX**) under analogous conditions led to the formation of a mixture of 1-fluoro-2,4-dimethyl- and 2-fluoro-1,3-dimethylbenzenes **X** and **XI** at a ratio of 1.4:1. A similar product ratio (1.8:1) was obtained previously in the fluorination of *m*-xylene with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4) in acetonitrile MeCN [26]; in addition, difluoro-substituted derivative, 1,5-difluoro-2,4-dimethylbenzene (**XII**), was formed in 23% yield. The overall yield of fluorinated products obtained from *m*-xylene was considerably lower than in the fluorination of mesitylene, other conditions being equal (Table 1), which may be related to lower reactivity of the former. Increase of the reaction time almost did not change the ratio of products **X** and **XI**, but the yield appreciably increased (Table 1).

The relative reactivity of durene and mesitylene is commonly used to distinguish between the classical polar mechanism involving formation of σ-complex (S_EAr) and single electron transfer (SET) mechanism implying intermediate radical cation (Scheme 2) [19, 27]. As applied to fluorination of aromatic compounds with N–F reagents, the relative contributions of the above mechanisms are likely to be determined by the nature of the substrate and reagent and reaction conditions. For example, high substrate selectivity was revealed in the competitive fluorination of mesitylene and durene with F-TEDA-BF_4 in acetonitrile or ionic liquid [emim][OTf] (k_{Mes}/k_{Dur} = 6 and 10, respectively at 80°C), which indicated polar mechanism of the process [19]. By contrast, the reverse reactivity ratio (k_{Mes}/k_{Dur} = 0.24) was observed in the fluorination of mesitylene and durene with the same reagent in aqueous acetonitrile; these data were interpreted in terms of the SET mechanism [27]. We examined the kinetics of competitive fluorination of mesitylene and durene with

Scheme 2.



Scheme 3.



XIII, **XVII** **XIV**, **XVIII** **XV**, **XIX** **XVI**

XIII–**XV**, R = H; **XVII**–**XIX**, R = Me.

NFSI in the absence of a solvent. The rate constant ratio k_{Mes}/k_{Dur} was estimated at 3.4 (105°C), indicating that the reaction follows polar mechanism.

Phenols and phenol ethers turned out to be fairly active in the fluorination with NFSI under solvent-free conditions. Fluorination of phenol (**XIII**) at 105°C (reaction time 3 h; substrate–reagent ratio 5:1) afforded mainly monofluoro derivatives **XIV** and **XV** at a ratio (*ortho*/*para*) of 1.2:1 (Scheme 3, Table 2). The regioselectivity in this reactions almost did not change as the temperature decreased. Reversal of the substrate–reagent ratio to 1:5 resulted in increased fractions of 2,4-difluorophenol (up to 8%) and 2-fluorophenol (*ortho*/*para* = 1.8:1).

The *ortho*/*para* ratios obtained in the fluorination of phenol with NFSI were similar (or even equal) to those observed in the fluorination of the same substrate with other N–F reagents in various solvents, e.g., with bis(4-fluoro-1,4-diazoniabicyclo[2.2.2]oct-1-yl)propane tetrakis(trifluoromethanesulfonate) in methanol (~1.5) [28], *N*,*N*′-difluoro-2,2′-bipyridinium bis(tetrafluoroborate) in acetonitrile (1.2) [29], and 1-fluoro-4-methyl-1,4-diazoniabicyclo[2.2.2]octane bis(trifluoromethanesulfonate) in methanol (~1.5) [30].

The overall yield of the fluorination products obtained from anisole (**XVII**) and NFSI at 105°C (no solvent) was considerably higher than in the fluorination of phenol (Table 2), but the *ortho*/*para* isomer ratio was almost the same (1.4) and similar to the isomer ratio observed in the fluorination of anisole with other N–F reagents in various solvents: 1-fluoro-1-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) in [emim][CF_3SO_3] (1.3) [19]; *N*,*N*′-difluoro-2,2′-bipyridinium bis(tetrafluoroborate) in acetonitrile (1.4) [29]; *N*-fluoroquinuclidinium trifluoromethanesulfonate in acetonitrile (1.5) [31]; F-TEDA-BF_4 in acetonitrile or trifluoroacetic acid (1.5 and 1.4, respectively) [32, 33]; 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) in acetonitrile (1.5) [32]; *N*-fluorobenzene-1,2-disulfonimide in $CDCl_3$ (1.5) [34]. These data suggest weak dependence of the regioselectivity on the nature of N–F reagent and polarity of the medium provided that specific effects are absent. The reverse *ortho*/*para*-isomer ratios were reported, e.g., for the fluorination with F-TEDA-BF_4 in strongly acidic medium (CF_3SO_3H, 0.8) [35] and with 2,4,6-trichloro-1-fluoro-1,3,5-triazinium tetrafluoroborate in nitromethane (0.5) [36]. Presumably, in the first case the reactive species is protonated trifluoromethanesulfonyl hypofluorite $SF_3SO_2OHF^+$ rather than F-TEDA-BF_4 [35], while in the second steric interaction between the methoxy group in the substrate and chlorine atoms in the reagent could hinder attack by the latter on the *ortho* position.

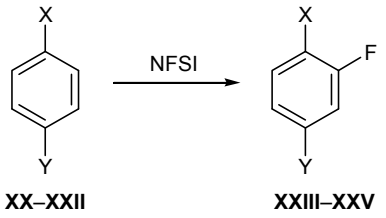
The reactions of NFSI with *p*-methylphenol (**XX**), 4-methylanisole (**XXI**), and 4-chloroanisole (**XXII**)

Table 2. Fluorination of phenol and anisole with *N*-fluorobenzenesulfonimide under solvent-free conditions

X in PhX	PhX–NFSI molar ratio	Temperature, °C	Time, h	Fractions of fluorination products, %			Overall yield, %
				ortho	*para*	2,4-F_2	
OH	5:1	105	3	55	44	1	56
OH	5:1	90	5	54	45	1	44
OH	5:1	80	3	56	44	–	47
OH	1:5	80	3	59	33	8	24
OMe	5:1	105	3	59	41	–	71
OMe	6:1	80	3	59	41	–	33

selectively afforded products of hydrogen replacement in the *ortho* position with respect to stronger electron-donating group (Scheme 4, Table 1).

Scheme 4.

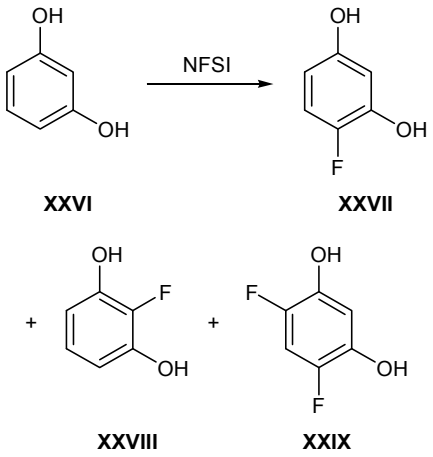


XX–XXII **XXIII–XXV**

XX, **XXIII**, X = OH, Y = Me; **XXI**, **XXIV**, X = OMe, Y = Me; **XXII**, **XXV**, X = OMe, Y = Cl.

The reaction of *p*-cresol (**XX**) with F-TEDA-BF_4 as more active N–F reagent in acetonitrile was accompanied by formation of an appreciable amount of 4-fluoro-4-methylcyclohexa-2,5-dien-1-one (in addition to phenol **XXIII**) [37]. Likewise, 4-fluorobenzene-1,3-diol (**XXVII**) was obtained with high selectivity by fluorination of resorcinol (**XXVI**) with NFSI; also, small amounts of 2-fluoro- and 4,6-difluorobenzene-1,3-diols **XXVIII** and **XXIX** were formed (Scheme 5, Table 1).

Scheme 5.

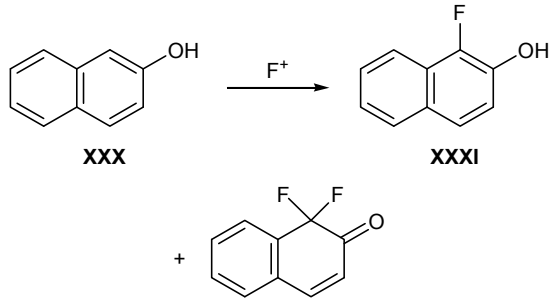


XXVI **XXVII** **XXVIII** **XXIX**

Analogous results were obtained previously using *N*,*N*′-difluoro-2,2′-bipyridinium bis(trifluoromethanesulfonate) in acetonitrile; in this case, 10% of 4,6-difluorobenzene-1,3-diol was also formed [29].

Fluorination of 2-naphthol (**XXX**) with N–F reagents in organic solvents is usually accompanied by formation of 1,1-difluoronaphthalen-2(1*H*)-one (**XXXII**) together with the corresponding monofluoro derivative, 1-fluoronaphthalen-2-ol (**XXXI**). The yield of ketone **XXXII** was 27% in the reaction with F-TEDA-BF_4 in acetonitrile [23], ~33% in the reaction with 1-fluoro-4-methyl-1,4-diazoniabicyclo[2.2.2]octane bis(trifluoromethanesulfonate) in methanol [30], ~33% in the reaction with *N*-fluoroquinuclidinium salts in acetonitrile [31], 18% in the fluorination with *N*,*N*′-difluoro-2,2′-bipyridinium bis(tetrafluoroborate) in formic acid [29], and 11% in the reaction with 3,5-dichloro-1-fluoropyridinium trifluoromethanesulfonate in methylene chloride [38] (Scheme 6). The fluorination of 2-naphthol with NFSI under solvent-free conditions yields 1-fluoronaphthalen-2-ol (**XXXI**) as the major product, and almost no ketone **XXXII** is formed (Table 1). This reaction is likely to begin in the solid phase, and the mixture turns liquid in 5 min.

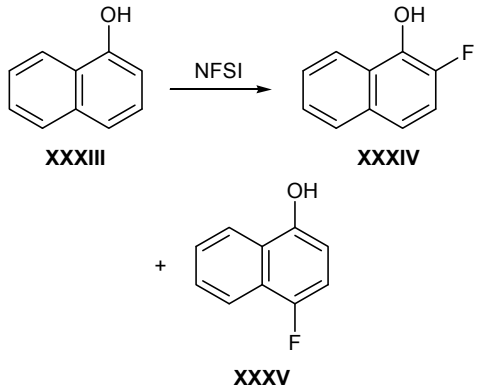
Scheme 6.



XXX **XXXI** **XXXII**

Likewise, no 2,2-difluoronaphthalen-1(2*H*)-one was detected among products of the reaction of 1-naphthol (**XXXIII**) with NFSI (cf. [23, 38]), and the main products were 2- and 4-fluoronaphthalen-1-ols **XXXIV** and **XXXV** at a ratio of 7 : 3 (Scheme 7, Table 1).

Scheme 7.



XXXIII **XXXIV** **XXXV**

Thus the fluorination of aromatic compounds with *N*-fluorobenzenesulfonimide under solvent-free conditions in some cases ensures higher selectivity than the use of other N–F reagents in solution.

EXPERIMENTAL

The ^{1}H and ^{19}F NMR spectra were recorded from solutions in $CDCl_3$ on a Bruker AV-300 spectrometer at 300 and 282.4 MHz, respectively. The chemical shifts were measured relative to the residual solvent signal ($CHCl_3$, δ 7.24 ppm) or $PhCF_3$ (internal reference, δ_F –63.73 ppm relative to $CFCl_3$). The mass spectra were obtained on an Hewlett–Packard G1800A GC–MS system consisting of an HP 5971 mass-selective detector and an HP 5890 Series II gas chromatograph. The structure of the obtained compounds was confirmed by the ^{1}H and ^{19}F NMR and mass spectra which were consistent with published data for 2-fluoro-1,3,5-trimethylbenzene, 2,4-difluoro-1,3,5-trimethylbenzene [39], 3-fluoro-1,2,4,5-tetramethylbenzene [39], 1-fluoro-2,3,4,5,6-pentamethylbenzene [40], 1-fluoro-2,4-dimethylbenzene, 2-fluoro-1,3-dimethylbenzene* [41], 2- and 4-fluorophenols [41–43], 2,4-difluorophenol [42], 2-fluoro-4-methylphenol [41], 2-fluoro-1-methoxy-4-methylbenzene, 4-chloro-2-fluoro-1-methoxybenzene [19], 2-fluorobenzene-1,3-diol, 4-fluorobenzene-1,3-diol, 4,6-difluorobenzene-1,3-diol [29, 44], 1-fluoronaphthalen-2-ol [31], 2- and 4-fluoronaphthalen-1-ols [23], and 2- and 4-fluoro-1-methoxybenzenes [19, 41].

The following reagents were used: *N*-fluorobenzenesulfonimide (>97%) and pentamethylbenzene (>99%) from Aldrich; anisole, *m*-xylene, and mesitylene of pure grade were distilled and dried over molecular sieves; durene (chemically pure), phenol (pure), and *p*-cresol (pure) were purified by sublimation; resorcinol (pure), 4-chloroanisole (pure), 1-naphthol (pure), and 2-naphthol (analytical grade). Deuterated solvents $CDCl_3$ and DMSO-d_6 contained 99 mol % of deuterium. 4-Methylanisole was synthesized according to the procedure described in [45].

Typical procedure for fluorination of aromatic compounds with *N*-fluorobenzenesulfonimide. Aromatic substrate, 0.65 mmol, and NFSI, 0.13 mmol, were mixed at room temperature in an NMR ampule** (or Teflon ampule), the mixture was kept as long as necessary at a required temperature, ~0.5 ml of $CDCl_3$ or $CDCl_3$– DMSO-d_6 (3:1) and $PhCF_3$ (internal reference) were added, and ^{1}H and ^{19}F NMR spectra were recorded. The yields and product ratios were calculated from signal intensities in the ^{19}F NMR spectra.

Competitive fluorination of mesitylene and durene with *N*-fluorobenzenesulfonimide. The reagent (NFSI) and substrates (mesitylene and durene) were mixed at a molar ratio of 1:5:5) at room temperature in a Teflon ampule, the mixture was heated for 35 min at 105°C and cooled, and $CDCl_3$–DMSO-d_6 mixture (3:1) was added. The ratio of the fluorinated products was determined from the intensities of the corresponding signals in the ^{19}F NMR spectrum.

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* In keeping with the ^{19}F NMR spectrum of compound **XI** from Maybridge, the chemical shifts of fluorine atoms in **X** and **XI**, given in [41], should be transposed.

** According to the ^{19}F NMR data, the reaction performed in a glass ampule was accompanied by formation of a small amount of unidentified product containing BF_4^- ion; the yield of the fluorination product was almost the same as in the reaction carried out in a Teflon ampule. Tetrafluoroborate ion was identified by addition of $Me_4N^+BF_4^-$ to the mixture.

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