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Eco-Friendly Fluorination of Aromatic Compounds with F-TEDA-BF_4 Reagent in Water

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Abstract

The interaction of bis(tetrafluoroborate) of 1-fluoro-4-chloromethyl-1,4-diazoniabicyclo[2.2.2]octane (F-TEDA-BF_4) with phenol, acetanilide and their derivatives, resorcinol, 1-, 2-naphthols and 6-methoxyquinoline in water was investigated. In some cases, fluorination of aromatic compounds in water proceeds more selectively than in the case when organic solvents are used.

Key words: NF reagent, electrophilic fluorination, selectivity, eco-friendly solvents, water, phenols, acetanilide and heteroaromatic compounds

INTRODUCTION

Fluorinated aromatic compounds find broad application as medicinal preparations (antibiotics, analgesics, antiseptics, antidepressants *etc.*), pesticides, and various functional materials. In this connection, development of ecologically acceptable and selective fluorination methods is urgent [1–4]. During the recent two decades, the sources of fluorine widely used for soft and selective fluorination of organic compounds are NF reagents, in particular 1-fluoro-4-chloromethyl-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4) [1–4]. This reagent is characterized by sufficient activity; it is convenient to work with, and well soluble in water which allows one to use it for the purpose of developing ecologically acceptable methods of fluorination. Water is a unique solvent; it is even called the matrix of life. Water is considered in the recent time as a promising and eco-friendly solvent to carry out diverse chemical reactions [5–7]. The advantage of water as solvent from the economical viewpoint is explained by its low cost in comparison with other solvents [7–9]. In addition, from the ecological point of view, water is a safe, inflammable, non-toxic solvent. Unique physical and chemical properties of water can be used to enhance the reactivity of compounds and the selectivity of chemical reactions [9]. However, in spite of these potential advantages, water does not find wide application as a solvent in organic chemistry, first of all because of the low solubility of the majority of organic compounds [8]. The data on the use of water for this purpose in fluorination of organic compounds are very limited [1–4, 10, 11].

The goal of the present work was to study the selectivity of fluorination of functionally substituted aromatic compounds using the F-TEDA-BF_4 reagent in water. The problem of selectivity in the electrophilic fluorination of aromatic compounds remains poorly studied [1].

EXPERIMENTAL

NMR ^1H and ^{19}F spectra were recorded with a Bruker AV-300 and AV-400 spectrometers. The internal standards in recording the NMR ^1H and ^{19}F spectra were residual protons of deuterochloroform (δ 7.24 ppm), deuteroacetone (δ 2.08 ppm) and C_6F_6 (δ_{CFCl_3} 162.9 ppm) or $C_6H_5CF_3$ (δ_{CFCl_3} 63.73 ppm), respectively. Exper-

iments with microwave heating were performed with the CEM Discover S-class set-up.

The structure of the synthesized compounds was confirmed by means of ^{1}H and ^{19}F NMR. Spectral characteristics corresponded to literature data: 2-fluoro-, 4-fluoro- [12, 14], 2,4-difluorophenol [13], 2-fluoro-, 4-fluoro-, 2,4-difluoroacetanilide [15, 16], 4-methyl-2-fluorophenol, 4-methyl-4-fluorocyclohexa-2,5-diene-1-on [12, 17], 4,4-difluorocyclohexa-2,5-diene-1-on [17], 2-fluoro-4-chlorophenol [14], 4-bromo-2-fluorophenol [14], 4-hydroxy-3-fluorobenzoic acid [18], 4-methoxy-3-fluorobenzoic acid [18], 4-methyl-2-fluoroacetanilide [15], 2-fluoro-, 4-fluoro-, 4,6-difluororesorcinol [19, 20], 2-fluoro-, 4-fluoro-1-naphthol, 2,4-difluoro-1-naphthol, 2,2-difluoro-1(2*H*)-naphthalinone [21, 22], 1-fluoro-2-naphthol, 1,1-difluoro-2(1*H*)-naphthalinone [23], 6-methoxy-5-fluoroquinoline, 5,5-difluoro-6(5*H*)-quinolinone [15, 24].

Reagents used in the work were: phenol, acetanilide, resorcinol, 1-, 2-naphthol, *p*-cresol, *p*-fluoro-, *p*-chloro-, *p*-bromophenols, *p*-hydroxy-, *p*-methoxybenzoic acids, *N*-acetyl-*p*-toluidine of ch. reagent grade (pure), 1-fluoro-4-chloromethyl-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate) (>95 %, Aldrich), 6-methoxyquinoline (>98 %, Lancaster), $CDCl_3$ and $(CD_3)_2CO$ with the atomic fraction of deuterium 99.8 and 99.5 %, respectively.

General procedure of fluorination using F-TEDA-BF_4 reagent in water and in H_2O—EtOH, H_2O—AcOH mixtures

The F-TEDA-BF_4 powder was added to the solution of 0.5 mmol of aromatic substrate in 5 mL of distilled water (the molar ratios of F-TEDA-BF_4/ArH are listed in Tables 1–3). The reaction mixture was kept at a definite temperature, cooled, extracted with Et_2O, the extract was dried with $MgSO_4$, ether was evaporated, the residue was dissolved in $CDCl_3$ or in deuteroacetone. After the addition of a weighted portion of *p*-bromobenzotrifluoride, NMR spectra were recorded. The yield and ratio of fluorination products were determined by means of NMR ^{19}F.

Reaction in the H_2O–EtOH mixture was carried out in a similar manner. After mixing was ceased, the solution was evaporated in vacuum to the half of its initial volume, and saturated with sodium chloride. The product was extracted with ether (5 × 2 mL), the extract was dried with sodium sulphate, and the solvent was removed in vacuum. The analysis of fluorination products was carried out using the procedure described above.

When reaction was carried out in the H_2O–AcOH mixture, reaction mixture was diluted with water, potassium carbonate was added for neutralization, and then the treatment was carried out according to the standard procedure.

TABLE 1

Fluorination of phenol and acetanilide with the F-TEDA-BF_4 reagent in water

Compounds	F-TEDA-BF_4/ArH	Temperature, °C	Time, h	Reaction products (yield, %)	*ortho*/*para*	Total yield, %
I	1.1 : 1	60	1.17	**I**-2F (34), **I**-4F (18), **I**-2,4F (6)	1.9	58
I	1.1 : 1	60*	0.08	**I**-2F (8), **I**-4F (5), **I**-2,4F (2)	1.6	15
I	1.2 : 1	25	24	**I**-2F (12), **I**-4F (8)	1.5	20
II	1.5 : 1	40	8	**II**-2F (19), **II**-4F (10), **II**-2,4F (2)	1.9	31
II	1.0 : 1	40	2	**II**-2F (5), **II**-4F (3), **II**-2,4F (0)	1.7	8
II	1.0 : 1	60	2	**II**-2F (22), **II**-4F (14), **II**-2,4F (2)	1.6	38
II	1.0 : 1	60	15	**II**-2F (33), **II**-4F (18), **II**-2,4F (3)	1.8	54
II	1.0 : 1	80	2	**II**-2F (33), **II**-4F (18), **II**-2,4F (2)	1.8	53
II	1.0 : 1	80*	0.5	**II**-2F (34), **II**-4F (20), **II**-2,4F (4)	1.7	58
II	1.0 : 1	100	0.08	**II**-2F (26), **II**-4F (15), **II**-2,4F (2)	1.7	43
II	1.0 : 1	100*	0.05	**II**-2F (35), **II**-4F (22), **II**-2,4F (4)	1.6	61

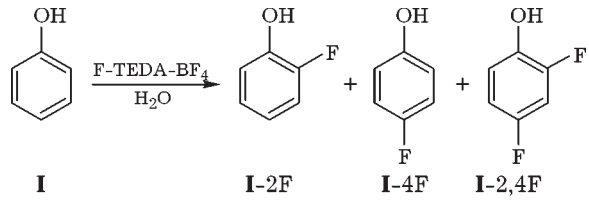
*Microwave irradiation was used.

Fluorination using microwave radiation

The F-TEDA-BF_4 powder was added to the solution of 0.5 mmol of aromatic substrate in 5 mL of the solvent. The reaction mixture was stirred in a closed tube 10 mL in volume at a given temperature under heating with the microwave radiation. The dynamic heating mode was used to perform the reaction. The power of magnetron was changed smoothly to maintain the necessary temperature. Sample temperature was controlled with the help of pyrometric sensors with the accuracy of ±1 °C. After the reaction was over, the mixture was treated and analysed as described above. The conditions of fluorination reaction are described in Tables 1–3.

RESULTS AND DISCUSSION

It was established that the prevailing products formed in fluorination of phenol (**I**) with the F-TEDA-BF_4 reagent in water are 2-fluoro- (**I**-2F), 4-fluoro- (**I**-4F) and 2,4-difluorophenols (**I**-2,4F) (see Table 1):



The relative fraction of the *para*-isomer increases slightly with a decrease in temperature and increase in reaction time. With the use of the microwave radiation, the selectivity of fluorination remains almost unchanged. A similar ratio of *ortho*/*para*-isomers was obtained previously using other NF reagents and solvents: 1-fluoro-4-chloromethyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (2.0, MeCN, 150 °C) [25], 1-fluoro-4-methyl-1,4-diazoniabicyclo-[2.2.2]octane bistriphlate (~1.5, MeOH, 20 °C) [26], 1,4-difluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) (2.4, HCOOH, 20 °C) [27], 1,1′-difluoro-2,2′-bipyri-

TABLE 2

Fluorination of di-substituted benzenes with the F-TEDA-BF_4 reagent in water

Compounds	X	Y	F-TEDA-BF_4/ArH	Temperature, °C	Time, h	Reaction products (yield, %)
III	1-OH	4-Me	1 : 1	20	20	**III**-2F (19), **X** (24)
III	1-OH	4-Me	1 : 1	60	2	**III**-2F (13), **X** (6)
IV	1-OH	4-F	1 : 1	20	48	**IV**-2F (25), **XI** (5)
IV	1-OH	4-F	1 : 1	80	1	**IV**-2F (17), **XI** (3)
IV	1-OH	4-F	1 : 1	100*	1	**IV**-2F (8), **XI** (3)
V	1-OH	4-Cl	1 : 1	40	15	**V**-2F (23)
V	1-OH	4-Cl	1 : 1	80	1	**V**-2F (25)
V	1-OH	4-Cl	1 : 1	100*	0.17	**V**-2F (14)
VI	1-OH	4-Br	1 : 1	60	6	**VI**-2F (20)
VI	1-OH	4-Br	1 : 1	100*	0.17	**VI**-2F (19)
VII	1-OH	4-COOH	1 : 1	100	1	**VII**-2F (19)
VII	1-OH	4-COOH	1 : 1	100*	1	**VII**-2F (20)
VIII	1-MeO	4-COOH	1 : 1	80	8	**VIII**-2F (13)
IX	1-NHAc	4-Me	1.5 : 1	60	15	**IX**-2F (17)
XII	1-OH	3-OH	1.1 : 1	20	24	**XII**-4F (36), **XII**-2F (2), **XII**-4,6F (5)
XII	1-OH	3-OH	1 : 1	40	6	**XII**-4F (39), **XII**-2F (2), **XII**-4,6F (5)
XII	1-OH	3-OH	1.5 : 1	40	6	**XII**-4F (43), **XII**-2F (2), **XII**-4,6F (6)
XII	1-OH	3-OH	1.1 : 1	80*	0.17	**XII**-4F (25), **XII**-2F (1), **XII**-4,6F (3)
XII	1-OH	3-OH	1.1 : 1	100	0.17	**XII**-4F (28), **XII**-2F (2), **XII**-4,6F (4)
XII	1-OH	3-OH	1.1 : 1	100*	0.08	**XII**-4F (39), **XII**-2F (2), **XII**-4,6F (9)

*Microwave irradiation was used.

TABLE 3

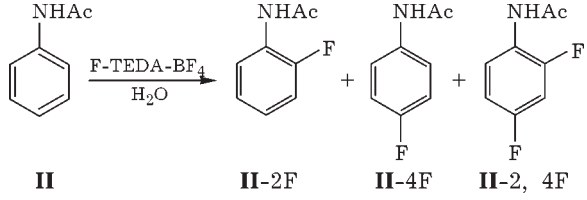
Fluorination of naphthols and 6-methoxyquinoline with the F-TEDA-BF_4 reagent in different media

Compounds	Medium	F-TEDA-BF_4/ArH	Temperature, °C	Time, h	Reaction products (yield, %)	Total yield, %
XIII	H_2O	1.0 : 1	40	15	**XIII**-2F (19), **XIII**-4F (14), **XII**-2,4F (2) **XIV** (8)	43
XIII	H_2O	1.5 : 1	40	20	**XIII**-2F (12), **XIII**-4F (10), **XII**-2,4F (3) **XIV** (11)	36
XIII	H_2O–EtOH	1.0 : 1	20	3	**XIII**-2F (27), **XIII**-4F (15), **XII**-2,4F (3) **XIV** (8)	53
XIII	H_2O–EtOH	2.0 : 1	20	3	**XIII**-2F (6), **XIII**-4F (0), **XII**-2,4F (6) **XIV** (28)	40
XV	H_2O	1.0 : 1	60	6	**XV**-1F (7), **XVI** (30)	37
XV	H_2O–EtOH	1.0 : 1	40	15	**XV**-1F (41), **XVI** (16)	57
XV	H_2O–EtOH	1.5 : 1	40	20	**XV**-1F (31), **XVI** (40)	71
XV	H_2O–EtOH	1.0 : 1	20	3	**XV**-1F (17), **XVI** (13)	30
XV	H_2O–EtOH	2.0 : 1	20	3	**XV**-1F (8), **XVI** (76)	84
XV	H_2O–AcOH	1.0 : 1	20	20	**XV**-1F (33), **XVI** (10)	43
XVII	H_2O	1.0 : 1	60	4	**XVII**-5F (4), **XVI** (16)	20
XVII	H_2O	1.1 : 1	80	12	**XVII**-5F (4), **XVI** (7)	11
XVII	H_2O–EtOH	1.0 : 1	100*	0.33	**XVII**-5F (11), **XVI** (15)	26

*Microwave irradiation was used.

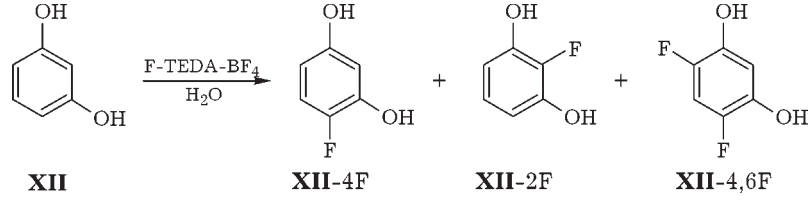
dinium bis(tetrafluoroborate) (1.2, MeCN, 80 °C) [20], 1,3-bis(4-fluoro-1,4-diazoniabicyclo-[2.2.2]octyl)propane bistriphlate (~1.5, MeOH, 20 °C) [28], N-fluorobis(trifluoromethylsulphonyl)amine (1.5, $CDCl_3$, 22 °C) [12]. Essentially higher *ortho*/*para*-isomers ratio observed with the use of substituted 1-fluoropyridinium-2-sulphonates is due to the specific interaction of SO_3^- groups of reagent and OH groups of phenol [29].

Fluorination of acetanilide (**II**) with F-TEDA-BF_4 reagent in water results in the prevailing formation of 2-fluoro- (**II**-2F), 4-fluoro- (**II**-4F) and 2,4-difluoroacetanilide (**II**-2,4F) (see Table 1):



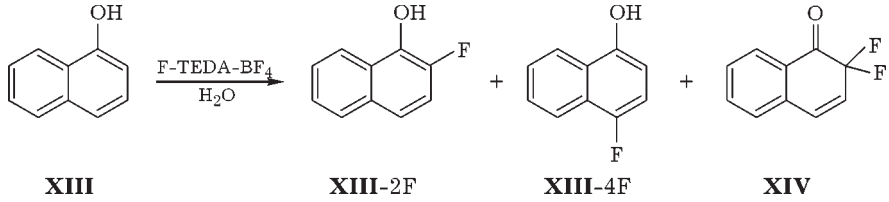
II **II**-2F **II**-4F **II**-2, 4F

The ratio of *ortho*/*para*-isomers is close to their ratio in the case of phenol fluorination. Variation of temperature and the reagent/substrate ratio does not lead to any substantial in-



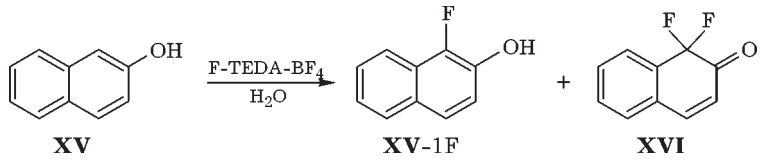
XII **XII**-4F **XII**-2F **XII**-4,6F

Scheme 1.

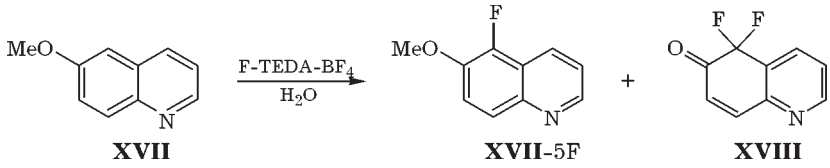


XIII **XIII**-2F **XIII**-4F **XIV**

Scheme 2.



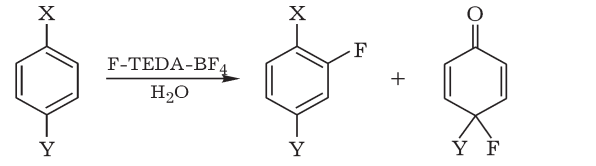
Scheme 3.



Scheme 4.

crease in the selectivity of reaction. Similar results were obtained previously using 1-methyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bistriphlate (~1.6, MeOH, 70 °C) [26].

Fluorination of *para*-substituted benzenes is performed rather selectively with the prevailing formation of the product of substitution at the ortho-position to the more donor group (see Table 2). In the case of *p*-cresol and *p*-fluorophenol also the products of *ipso*-fluorination (**X**) and (**XI**) are formed, while for other phenols with Y = Cl, Br, COOH groups the products of that kind were not detected.



X = OH, Y = Me (**III**), F (**IV**), Cl (**V**), Br (**VI**), COOH(**VII**)
X = MeO, Y = COOH(**VIII**)
X = NHAc, Y = Me (**IX**)

Y = Me (**X**), F (**XI**)

Fluorination of resorcinol in water proceeds selectively with the prevailing formation of 4-fluororesorcinol. Along with this, small amounts of 2-fluororesorcinol and 4,6-difluororesorcinol were revealed (see Scheme 1, Table 2).

A decrease in temperature and the use of microwave radiation do not have a substantial effect on the selectivity of the reaction. It should be noted that fluorination of resorcinol with the F-TEDA-BF_4 reagent in MeCN resulted in the formation of a complicated mixture of products [30].

Fluorination of 1-naphthol in water gives mainly 2-fluoro-1-naphthol (**XIII**-2F), 4-fluoro-1-naphthol (**XIII**-4F) and 2,2-difluoro-1(2*H*)-naphthalinone (**XIV**) (Scheme 2). An increase in reaction time does not have any substantial effect on its selectivity. Similar product ratio was observed after fluorination of 1-naphthol with F-TEDA-BF_4 reagent in MeCN at a temperature of 20 °C (**XIII**-2F : **XIII**-4F : **XIV** = 49 : 41 : 10) [21].

Fluorination of 2-naphthol (**XV**) with F-TEDA-BF_4 reagent in water or in H_2O–EtOH (1 : 1), H_2O–AcOH (1 : 1) mixtures results in the prevailing formation of 1-fluoro-2-naphthol (**XV**-1F) and 1,1-difluoro-2(1*H*)-naphthalinone (**XVI**); an increase in F-TEDA-BF_4/ArH ratio leads to an increase in the relative fraction of the ketone (Scheme 3).

Fluorination of 6-methoxyquinoline (**XVII**) with F-TEDA-BF_4 reagent in water leads along with the product of the substitution of hydrogen atom by fluorine (**XVII**-5F) to the formation of ketone (**XVIII**) (Scheme 4).

CONCLUSION

Thus, water is a promising eco-friendly solvent for carrying out fluorination of functionally substituted aromatic and heteroaromatic compounds by NF reagents. In some cases, fluorination of aromatic compounds in water proceeds more selectively than in organic solvents. The use of microwave radiation does not have substantial influence on the selectivity of fluorination of aromatic compounds.

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