# Fluorination of aromatic compounds with xenon difluoride in the presence of boron trifluoride etherate*

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Fluorination of benzene with the $XeF_2$—$BF_3 \cdot Et_2O$ system in acetonitrile at low temperatures affords fluorobenzene in 18% yield, the conversion of benzene being 92%. The rest products are di-, tri-, tetra-, and polyphenyls with different fluorination pattern. Toluene and chloro- and bromobenzenes are fluorinated predominantly at the *ortho* and *para* positions. Fluorination of 4-nitroanisole affords 2-fluoro-4-nitroanisole in 73% yield.

**Key words:** xenon difluoride, boron trifluoride etherate, fluorobenzene, fluoroarenes, organofluorine compounds.

Earlier, xenon difluoride was proposed for fluorination of organic compounds.[1] This reagent offers a number of advantages over elemental fluorine (solid state, low toxicity). The reaction of $XeF_2$ with aromatic aldehydes and ketones affords difluoromethyl phenyl ethers,[1] while the use of trifluoroacetic acid as a solvent brings about trifluoromethylation products.[2]

Fluorination of benzene (**1**) with $XeF_2$ at room and higher temperatures in tetrachloromethane using HF as the catalyst affords a mixture of products with a fluorobenzene (**2**) content up to 68%; however, the benzene conversion is only 12% (per one cycle).[3] Fluorination of other aromatic compounds under similar conditions proceeds with a low selectivity.[4—7]

Boron trifluoride diethyl etherate (BTFE) is an available Lewis acid used as the catalyst for electrophilic aromatic substitution. It has been applied earlier in $XeF_2$ fluorination of perfluoroarenes to perfluorocyclohexane derivatives,[8] as well as in fluorination of fluorene and benzofuran to the corresponding monofluorinated derivatives.[9]

The aim of the present work is to study whether it is possible to raise the selectivity of $XeF_2$ fluorination of aromatic compounds at low temperature using BTFE as the catalyst.

## Results and Discussion

It was found that benzene underwent no fluorination in the absence of catalyst below 10 °C in either $CH_2Cl_2$ or MeCN and, on raising the temperature to ~20 °C, after a time the reaction proceeds in a vigorous and uncontrolled manner to form resinous products.

In the presence of catalytic amounts (1—10 mol.%) of BTFE using MeCN as the solvent, formation of fluorobenzene was observed; however, the conversion was low and depended only on the amount of BTFE added. Prolongation of the reaction time and two-fold increase in the amount of $XeF_2$ did not improve the yield of fluorobenzene to cause only an increased resinification. We succeeded in raising the benzene conversion up to 92% to obtain fluorobenzene in 18% yield when benzene, BTFE, and $XeF_2$ were used in the molar ratio of 1 : 1.4 : 1.25, respectively. According to the data from mass spectrometry, the remaining products were di-, tri-, tetra-, and polyphenyls with different fluorination pattern whose formation agrees with the earlier proposed reaction mechanism[10] (Scheme 1).

The necessity for using BTFE in the amount exceeding the molar ratio is likely caused by its binding to HF evolved during fluorination to form tetrafluoroboric acid. The attempts to scavenge the released HF using organic (pyridine) and inorganic ($K_2CO_3$) bases inhibited the reaction completely even on boiling.

The reaction pathway also depends significantly on the reaction temperature. For example, the reaction proceeds very slowly below −38 °C and quite vigorously above −20 °C. The optimum conditions were effective cooling and slow addition of $XeF_2$ to avoid temperature rise above −25 °C.

The optimized procedure was used for fluorination of other arenes (see Scheme 1). Under these conditions, toluene (**3**) reacts readily with $XeF_2$ to form (according to the data from GLC and $^1H$ and $^{19}F$ NMR spectroscopy)

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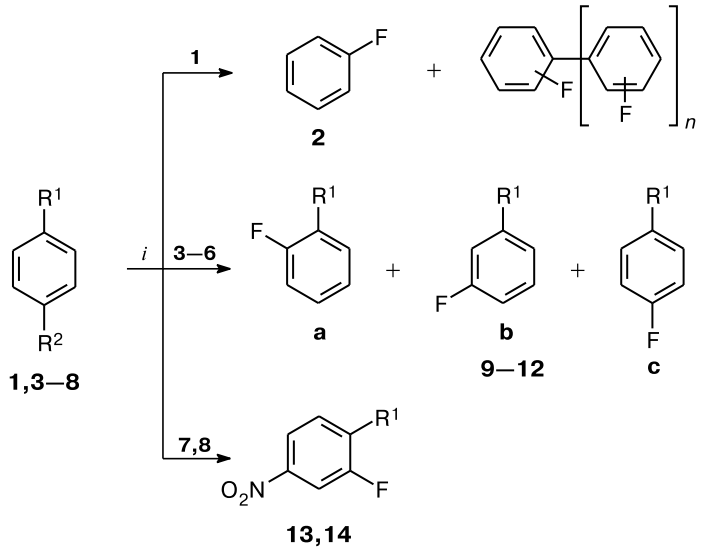
**Scheme 1**




| Compound | $R^1$ | $R^2$ | Compound | $R^1$ | $R^2$ | Compound | $R^1$ | Compound | $R^1$ |
|---|---|---|---|---|---|---|---|---|---|
| **1** | H | H | **6** | $NO_2$ | H | **9** | Me | **12** | $NO_2$ |
| **3** | Me | H | **7** | Me | $NO_2$ | **10** | Cl | **13** | Me |
| **4** | Cl | H | **8** | OMe | $NO_2$ | **11** | Br | **14** | OMe |
| **5** | Br | H | | | | | | | |

$n$ = 1, 2, 3...

**Reagents and conditions:** *i.* 1) $XeF_2$, $BF_3 \cdot Et_2O$, MeCN, –30 °C; 2) $NaHCO_3$, $H_2O$.

a mixture of three isomers **9a—c** in the following ratio: 62% of **9a** (*ortho* isomer), 9% of **9b** (*meta* isomer), and 29% of **9c** (*para* isomer) (Table 1). The overall yield of fluorobenzenes after distillation was 21% at the toluene conversion of 94%, the distillation residues being high-molecular-weight resinification products.

Chlorobenzene (**4**) and bromobenzene (**5**) reacted similarly (see Table 1). The ratio of isomeric chlorofluorobenzenes **10a—c** was almost the same as in the case of toluene fluorination: 63% of **10a**, 8% of **10b** and 29% of **10c**. In the case of bromofluorobenzenes **11a—c**, the ratio of *ortho* and *para* isomers changed compared to fluorotoluenes to be 29% (**11a**) and 62% (**11c**), respectively. This is likely due to the steric effect of bromine atom which hinders the *ortho* position. The yield of *meta* isomer **11b** is virtually equal to those of fluoro derivatives **9b** and **10b**.

It should be noted that Ref. 4 gives higher yields of fluorination products of arenes, but discusses neither conversion nor amounts of compounds isolated. Our procedure allows less laborous preparation of fluoroarenes in comparable yields.

Fluorination of nitrobenzene (**6**) under these conditions proceeds very slowly, according to the $^1H$ and $^{19}F$ NMR spectral data the yield of fluoronitrobenzenes **12a—c** was

**Table 1.** Yields and $^{19}F$ NMR spectra of compounds **9—14**

| Compound | Yield (%) | Degree of starting compound conversion (%) | Ratio of *o* : *m* : *p* isomers | $\delta_F$* | | |
|---|---|---|---|---|---|---|
| | | | | *ortho*-Isomer (**a**) | *meta*-Isomer (**b**) | *para*-Isomer (**c**) |
| **9a—c** | 21 | 94 | 62 : 9 : 29 | –118.61 (–117.30)[11] | –114.98 (–113.70)[11] | –119.27 (–118.00)[11] |
| **10a—c** | 42 | 99 | 63 : 8 : 29 | –116.34 (–115.60)[11] | –111.47 (–110.30)[11] | –117.15 (–117.38)[11] |
| **11a—c** | 56 | 99 | 29 : 9 : 62 | –108.91 (–108.20)[11] | –111.16 (–110.00)[11] | –115.86 (–115.47)[11] |
| **12a—c** | 6 | 10 | 9 : 89 : 2 | –120.30 (–119.00)[11] | –110.75 (–109.50)[11] | –103.61 (–102.40)[11] |
| **13** | 10 | 13 | — | –114.41 (–113.40)[12] | — | — |
| **14** | 73 | 76 | — | –132.90 (–131.40)[12] | — | — |

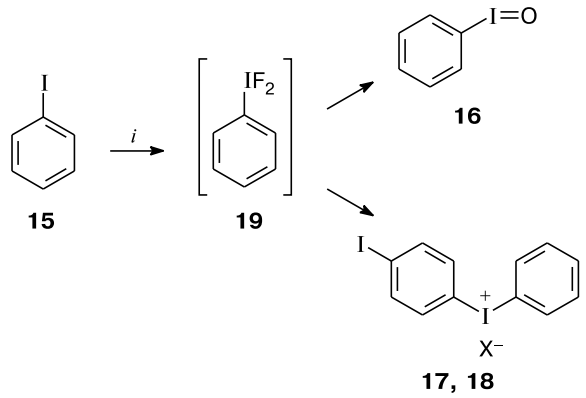
* Given in parentheses are literature data.

~6% at the total nitrobenzene conversion of 10%. It should be noted that, although *meta*-fluoronitrobenzene (**12b**) accounts for 90% of fluoronitrobenzenes, the ratio of *ortho*/*para* isomers (**12a**/**c**) was 5 : 1, which is quite unusual. Fluorination of 1-methyl-4-nitrobenzene (**7**) also resulted in a low yield (~10%) of 2-fluoro-1-methyl-4-nitrobenzene (**13**) at the total degree of conversion of the starting compound of 13%. At the same time, fluorination of the more reactive 1-methoxy-4-nitrobenzene (**8**) afforded 2-fluoro-1-methoxy-4-nitrobenzene (**14**) in 73% yield and the total conversion of compound **8** was 76%, which was likely caused by the activating effect of methoxy group.

It should be noted that the formation of polyphenyls in such processes took place only in the case of benzene (**1**).

Iodobenzene (**15**) reacted in a unique manner under optimized conditions (Scheme 2). The analysis of reaction products of iodobenzene with $XeF_2$ in the presence of compound **2** showed that the resulted mixture of products consists of 76% of iodobenzene (**16**) and 24% of (4-iodophenyl)(phenyl)iodonium tetrafluoroborate (**17**). It is known that the related (4-iodophenyl)(phenyl)iodonium triflate (**18**) is obtained by the exposure of benzene, iodine, and iodobenzene to oxidizing agents[13,14] or by the direct reaction between iodobenzene and iodosobenzene[15] or diacetoxyiodosobenzene in the presence of trifluoromethanesulfonic acid.[16] Tetrafluoroborate **17** has been prepared earlier by the reaction between phenylboronic acid, iodobenzene, and MCPBA in the presence of BTFE (see Ref. 11).

**Scheme 2**




X = $BF_4$ (**17**), $CF_3SO_3$ (**18**)

**Reagents and conditions:** *i.* 1) $XeF_2$, $BF_3 \cdot Et_2O$, MeCN, −30 °C; 2) $NaHCO_3$, $H_2O$.

Probably, on contact with $XeF_2$, iodobenzene undergoes double fluorination at the iodine atom and, then, the resulted compound **19** reacts with excessive iodobenzene to form product **17**. The formation of iodosobenzene **16** is likely caused by the hydrolysis of compound **19** under the action of aqueous $NaHCO_3$ (see Scheme 2).

Thus, the reaction of aromatic compounds with $XeF_2$—BTFE system requires a great excess of BTFE. Even at low temperatures the reaction proceeds unselectively and, as judged by the ratio of isomers, complies with the rules of electrophilic aromatic substitution in monosubstituted benzenes. However, one should note some deviations from the rule in the case bromobenzene, which is likely due to steric factors. The nitro group significantly retards fluorination and the activating effect of such electron-donating group as the methyl one is insufficient for complete overcoming the deactivation. However, introduction of the methoxy group already allows overcoming the effect of highly ring-deactivating groups. Selection of the corresponding disposition of different substituents in the molecule can allow achieving high yields and selectivities upon fluorination of aromatic compounds with $XeF_2$.

## Experimental

Commercially available reagents were used for syntheses. The commercially available MeCN was kept for 1 day over phosphorus pentoxide (20 g per 1 L of MeCN), additional portion of the pentoxide (20 g) was added, and the mixture was refluxed for 1 h and distilled. The resulted distillate was fractionated over calcined $K_2CO_3$. The reaction product composition was controlled by GLC on a LKhM-8D chromatograph equipped with a catharometer (stainless steel column 5000×3 mm, the stationary phase was 8.5% diethylene glycol succinate on Chromaton, 80—100 mesh, the carrier gas was helium, the detector temperature was 250 °C, and the injector temperature was 300 °C). The column temperature was varied to be on average the half of the boiling point of starting aromatic compound. $^1H$ and $^{19}F$ NMR spectra were recorded on a Bruker Avance 11 300 spectrometer (300 and 282 MHz, respectively) in DMSO-$d_6$.

**General procedure for fluorination.** A three-necked flask equipped with an argon inlet and thermometer was loaded with arene **1** or **3**—**8** (10 mmol) in dry MeCN (15 mL). Then, BTFE (2.0 g, 14 mmol) was added. The mixture was cooled in the argon stream down to −35 °C and $XeF_2$ (2.05 g, 12.5 mmol) was added in small portions. The mixture was warmed to −25 °C, stirred for 30 min at this temperature, then heated to 20 °C for 1 h, and stirred for additional 1 h (GLC control). A saturated solution of sodium bicarbonate was added to the reaction mass until termination of gas evolution. The resulted mixture was extracted with diethyl ether (3×20 mL). The extract was washed with water and dried with sodium sulfate.

In the case of benzene (**1**), toluene (**3**), and chlorobenzene (**4**), the diethyl ether extracts were subjected to molecular distillation and fractionated, each fraction was analyzed by GLC and NMR spectroscopy. In the case of bromobenzene (**5**), nitrobenzene (**6**), *p*-nitrotoluene (**7**), and *p*-nitroanisole (**8**), the ethereal extracts were evaporated *in vacuo* at the temperature below 25 °C, the residue was dissolved in chloroform and subjected to flash chromatography (the eluent was hexane—chloroform, 3 : 1). The eluent was concentrated under normal pressure and the residue was analyzed by NMR spectroscopy.

In the case of iodobenzene (**15**), a precipitate formed upon neutralization with a solution of sodium bicarbonate was filtered, washed with water, sequentially with MeCN (5 mL) and

$Et_2O$ (5 mL) preserving the filtrate, and dried in air to yield a solid residue (1.1 g), which according to the NMR spectral data was a mixture consisting of (based on the weight percentages) 76% of iodosobenzene (**16**) and 24% of (4-iodophenyl)phenyliodonium tetrafluoroborate (**17**). Evaporation of the organic filtrate followed by the treatment of the residue with $CHCl_3$ affords 100 mg of compound **18** with m.p. 149 °C (*cf.* Ref. 17: 147—149 °C). $^1$H NMR (DMSO-$d_6$), δ: 7.59 (m, 3 H); 7.91 (d, 2 H, $J$ = 7.3 Hz); 8.02 (d, 2 H, $J$ = 7.3 Hz); 8.23 (d, 2 H, $J$ = 7.1 Hz). $^{19}$F NMR, δ: −149.05 $(BF_4)^-$.

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