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K. I. Petko^{1,2}, A. A. Filatov^{1,2}, O. O. Yurchenko¹, O. V. Volokitin¹

¹Institute of Organic Chemistry of the National Academy of Sciences of Ukraine,
5 Akademik Kuhar str., 02094 Kyiv, Ukraine

²Enamine Ltd., 78 Winston Churchill str., 02094 Kyiv, Ukraine

A Competitive Substitution of the Difluoromethoxy Group in Aminodehalogenation Reactions of Aromatic Nitro Compounds

Abstract

The interaction of substituted nitrobenzenes containing activated halogen atoms (fluorine or chlorine) and the difluoromethoxy group with an aqueous solution of ammonia at high pressure and temperature of 80–160 °C was studied. It has been found that under the conditions studied, the difluoromethoxy group can be replaced by the amino group as a pseudohalogen. It has been shown that the reactivity of the difluoromethoxy group in the same positions is lower than that of the fluorine atom, but significantly higher than that of the chlorine atom.

Keywords: difluoromethoxynitrobenzenes; difluoromethoxy group; amination; nucleophilic substitution

К. І. Петко^{1,2}, А. А. Філатов^{1,2}, О. О. Юрченко¹, О. В. Волокітін¹

¹Інститут органічної хімії Національної академії наук України,
вул. Академіка Кухаря, 5, м. Київ, 02094, Україна

²ТОВ НВП «Енамін», вул. Вінстона Черчилля, 78, м. Київ, 02094, Україна

Конкурентне заміщення дифторметокси групи в реакціях амінодегалогенування ароматичних нітросполук

Анотація

Досліджено взаємодію заміщених нітробензенів, що містять активовані атоми галогенів (фтору або хлору) і дифторметокси групи, з водним розчином амоніаку за високого тиску та температури 80–160°C. З'ясовано, що за досліджуваних умов дифторметокси група може поставати як псевдогалоген і її можна замінити аміногрупою. Виявлено, що реакційна здатність дифторметокси групи в тих самих положеннях нижча, ніж в атома фтору, але значно вища, ніж в атома хлору.

Ключові слова: дифторметоксинітробензол; дифторметокси група; амінування; нуклеофільне заміщення

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■ Introduction

The difluoromethoxy group has recently become quite readily available, and compounds containing it are often considered as promising bioactive agents [1]. Prominent examples include approved drugs Pantoprazole and Foridon containing the OCHF_2 group in their molecules (Figure 1).

In previous studies, the difluoromethoxy group in aromatic compounds was considered relatively stable, and no cases of the nucleophilic substitution of this group were described. Interestingly that the cases of the nucleophilic substitution of a closely related trifluoromethoxy group in an aromatic ring are known [2], and even cases of the methoxy group substitution were described [3].

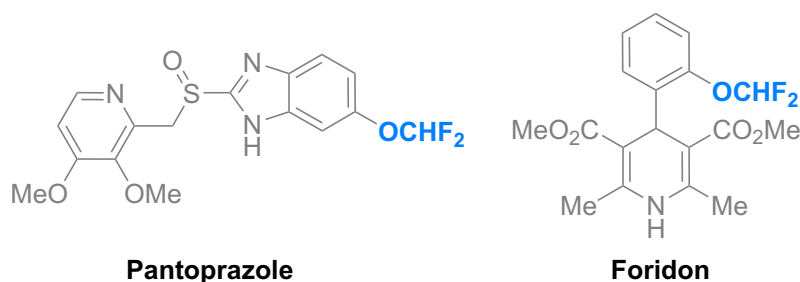
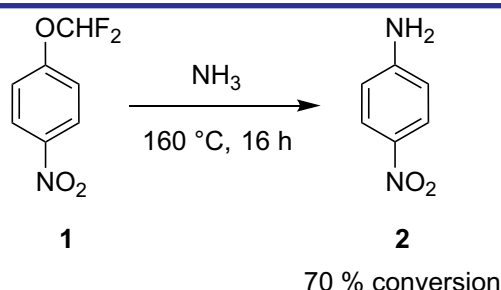


Figure 1. Drugs with a difluoromethoxy group

During nucleophilic substitution reactions involving halogenated benzene rings bearing a difluoromethoxy group, we repeatedly observed impurities resulting from the substitution of the difluoromethoxy group rather than the halogen atom. The reaction of the model compound, 4-nitrodifluoromethoxybenzene (**1**), with 25% aqueous ammonia at 160 °C for 16 h led to the formation of *para*-nitroaniline (**2**) with an approximate conversion of 70%. Simultaneously, other reaction products, such as 4-nitrophenol or 4-difluoromethoxyaniline, were not observed (**Scheme 1**).

Therefore, we considered a systematic study of the behavior of the difluoromethoxy group as a potential leaving group during the nucleophilic substitution of activated halogens in aromatic rings to be a relevant and important task for synthetic organic chemistry.

Scheme 1. The substitution of the OCHF₂ group in the model compound

■ Results and discussion

The starting compounds selected were halonitrobenzenes containing a difluoromethoxy group in the *para*-position to the nitro group, namely 2-chloro-4-(difluoromethoxy)-1-nitrobenzene (**3**), 1,4-dichloro-2-(difluoromethoxy)-5-nitrobenzene (**4**) and 1-chloro-2-(difluoromethoxy)-4-fluoro-5-nitrobenzene (**5**), as well as halonitrobenzenes containing a difluoromethoxy group in the *ortho*-position, namely 4-chloro-2-(difluoromethoxy)-1-nitrobenzene (**6**), 2-(difluoromethoxy)-4-fluoro-1-nitrobenzene (**7**), 1-chloro-3-(difluoromethoxy)-2-nitrobenzene (**8**) and 1-(difluoromethoxy)-3-fluoro-2-nitrobenzene (**9**) (**Figure 2**). Aqueous 25% ammonia was chosen as a model nucleophile.

Compounds **3**, **6**, and **8** were previously reported [4–6]. Nitroarenes **4** and **5** were synthesized *via* the nitration of the corresponding haloaryldifluoromethyl ethers **10a** and **10b** (**Scheme 2, A**). Compounds **7** and **9** were obtained through the difluoromethylation of phenols **11** and **12** using chlorodifluoromethane (**Scheme 2, B, C**). Due to the presence of an activated fluorine atom, these substrates could not be difluoromethylated under standard strongly basic conditions at 60–70 °C, as described in [7]. Therefore, we employed milder reaction conditions, performing the transformation at 30–35 °C in a THF/water

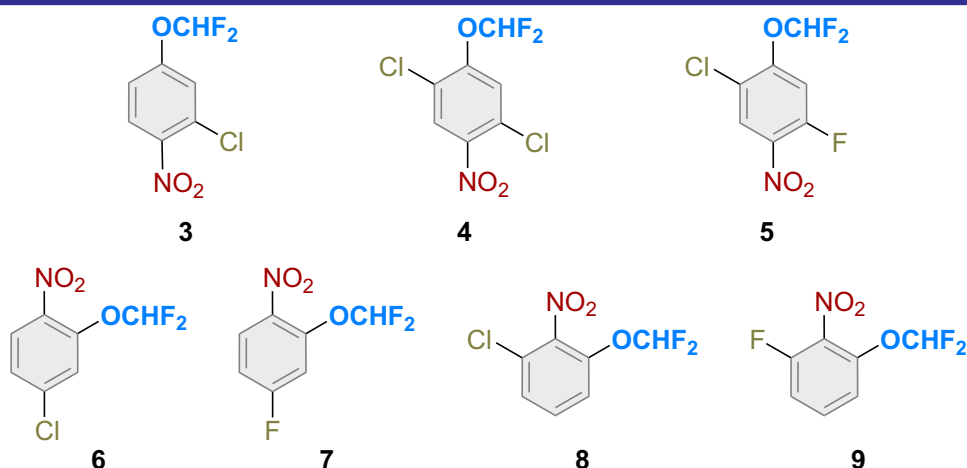
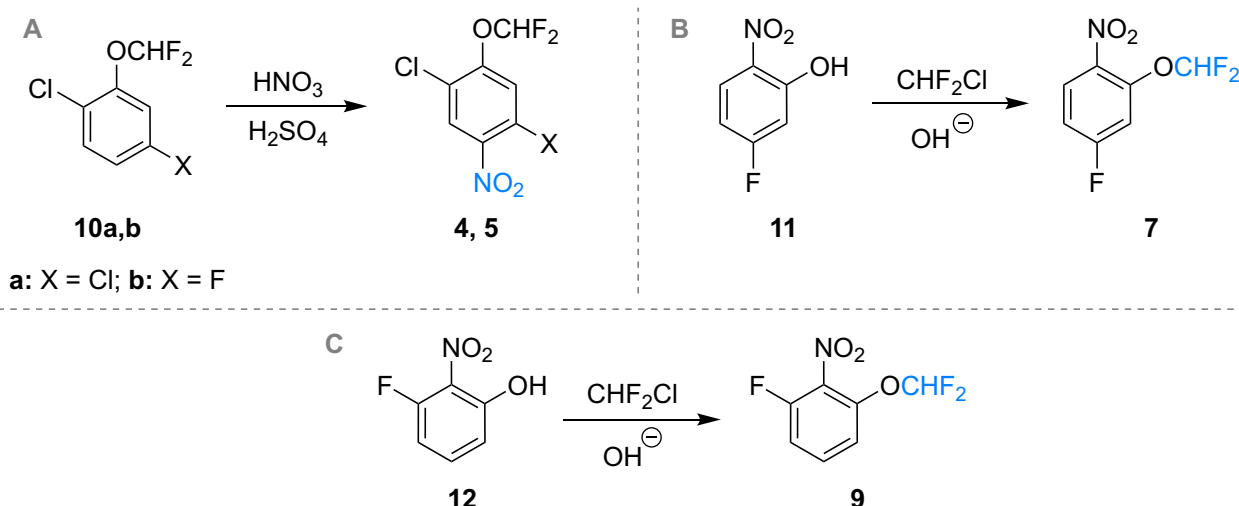


Figure 2. Starting compounds



Scheme 2. The synthesis of starting compounds

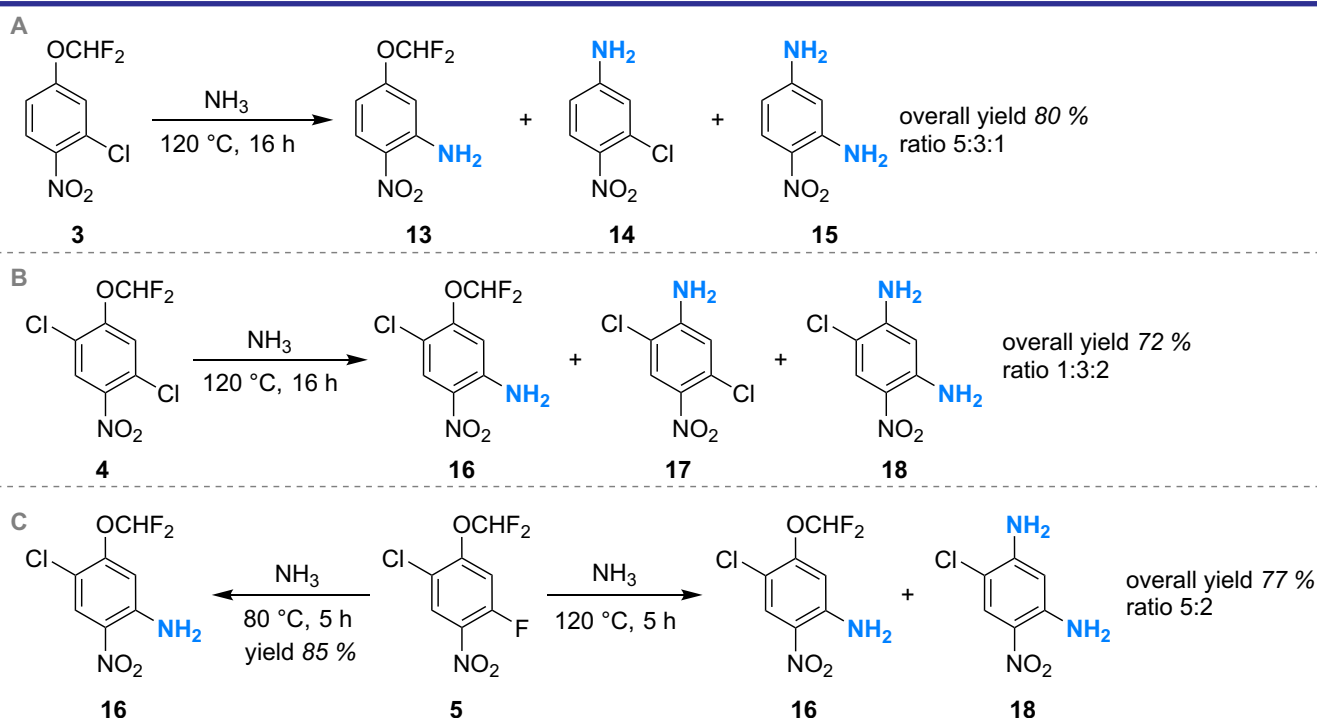
alkaline medium in the presence of a phase-transfer catalyst.

In the case of compounds **3–5**, the halogen atom was in the *ortho*-position to the nitro group and was therefore more activated towards the nucleophilic substitution (due to both inductive and mesomeric effects) compared to the *para*-difluoromethoxy group. The interaction of **3** and **4** with aqueous ammonia in a high-pressure reaction vessel occurred at 120°C and led to product mixtures (Scheme 3). In each case, the formation of three products – difluoromethoxy nitroanilines **13** or **16** (the chlorine atom substitution), chloronitroanilines **14** or **17** (the difluoromethoxy group substitution), and *meta*-phenylenediamines **15** or **18** (the simultaneous substitution

of both the chlorine atom and the difluoromethoxy group) were observed.

The presence of a chlorine atom in position 5 promoted the substitution of the difluoromethoxy group. Thus, when compound **3** was reacted with aqueous ammonia under the conditions studied, product **13** was obtained in a higher yield than product **14** (Scheme 3, A). In contrast, for the starting compound **4**, the major product was compound **17**. When the reaction was carried out at 160°C in both cases, the complete double substitution occurred, giving products **15** and **18**, respectively, in the yield approximately 65–70% (Scheme 3, A and B).

As expected, the substitution of the fluorine atom in compound **5** proceeded more readily.

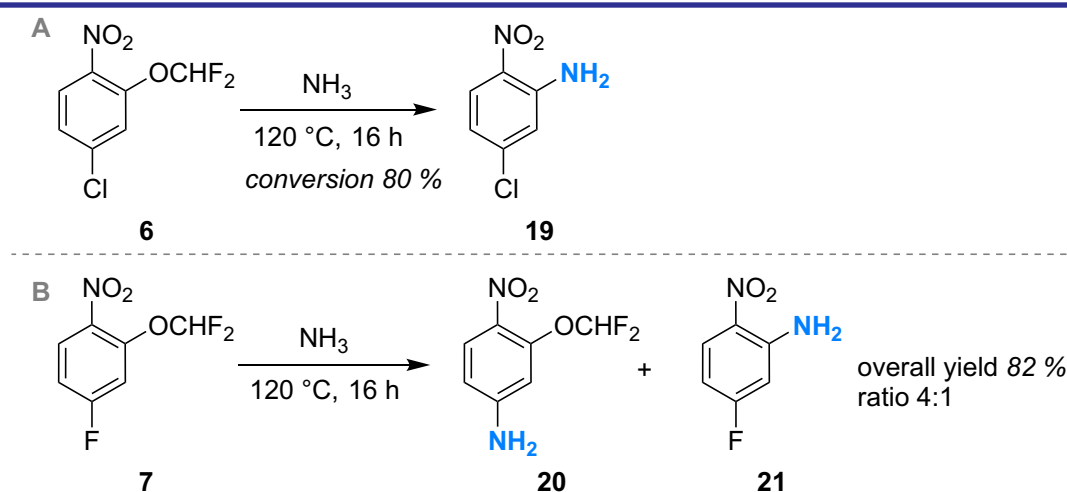
Scheme 3. The aminodehalogenation of nitrobenzenes with the difluoromethoxy group in the *para*-position

The reaction reached the complete conversion within 6 h at 80°C without affecting the difluoromethoxy group. However, performing the reaction at 120°C over the same time period resulted in a mixture of monosubstituted and double substituted products in a ratio of 5:2 (**Scheme 3, C**).

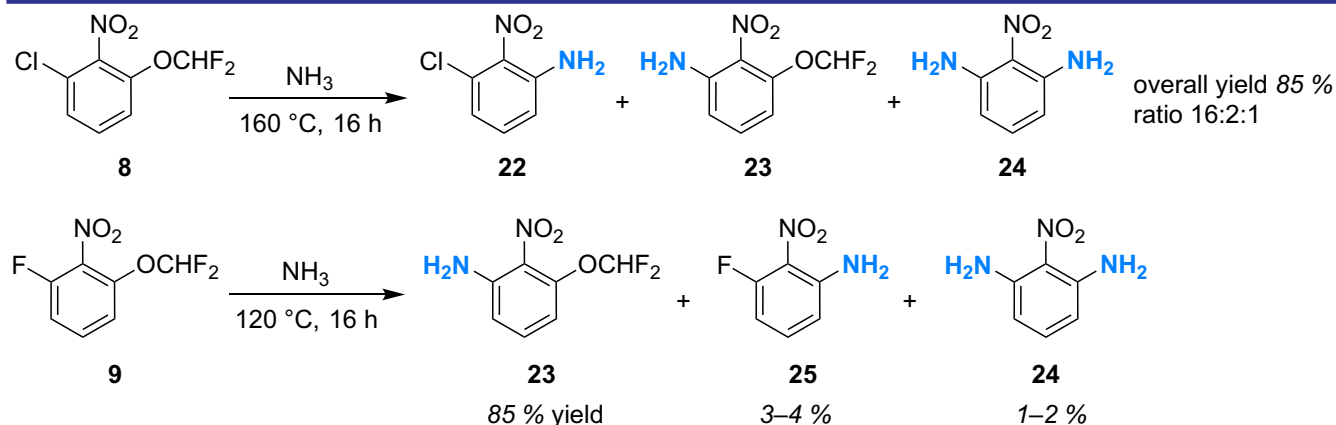
In the case of compounds **6** and **7**, the halogen atom was in the *para*-position to the nitro group and was therefore less activated towards the nucleophilic substitution compared to the difluoromethoxy group, which was in the *ortho*-position.

The reaction of compound **6** at 120°C did not lead to the substitution of the chlorine atom, but instead resulted exclusively in the substitution of the difluoromethoxy group, yielding compound **19** as the sole product (**Scheme 4, A**). In 16 h, the conversion reached approximately 80%. Under the same conditions, the reaction of compound **7** containing a fluorine atom proceeded to the complete conversion within this time frame and produced a mixture of fluorine-substituted product **20** and difluoromethoxy-substituted product **21** in a ratio of 4:1 (**Scheme 4, B**).

To reliably assess the relative reactivity of the halogen atom and the difluoromethoxy group, substrates, in which both substituents occupied the same (*ortho*) positions, were most suitable. Therefore, we studied compounds **8** and **9** with these groups in the *ortho*-position. The reaction of compound **8** with aqueous ammonia proceeded very slowly at 120°C; after 6 h of heating in a high-pressure vessel, NMR spectra showed virtually no signals corresponding to substitution products. However, conducting the reaction at 160°C led to a mixture, in which product **22** (resulting from the substitution of the difluoromethoxy group) was approximately 8 times more abundant than product **23** (resulting from the chlorine substitution). Additionally, the NMR analysis revealed the presence of a minor amount of double-substitution product **24**. These results clearly indicated that the difluoromethoxy group was substituted much more readily than the chlorine atom when both were located at an equivalent position. As expected, the reaction of fluoronitrobenzene **9** proceeded almost exclusively to give compound **23**



Scheme 4. The aminodehalogenation of nitrobenzenes with a halogen atom in the *para*-position and the difluoromethoxy group in the *ortho*-position



Scheme 5. The aminodehalogenation of nitrobenzenes with a halogen atom and the difluoromethoxy group in the *ortho*-position

in the yield of approximately 85%. According to NMR data, minor impurities of the fluorine-substituted product **25** and the double-substituted product **24** did not exceed 5–6% and were not isolated (Scheme 5).

■ Conclusions

Thus, we have studied the dehaloamination of various nitrobenzenes containing activated halogen atoms (fluorine and chlorine) and the difluoromethoxy group with aqueous ammonia in an autoclave at 80–160°C. The dependencies of the ratio of substitution products on the position of leaving groups (halogen or difluoromethoxy group) have been found. It has been shown that in the presence of the difluoromethoxy group in nitrobenzene, the nucleophilic substitution of halogen occurs unambiguously only in the case of an activated fluorine atom, whereas the chlorine atom is replaced significantly more slowly than the difluoromethoxy group.

■ Experimental part

Melting points were measured in an open capillary and were given uncorrected. ^1H NMR (300 MHz, CDCl_3) spectra, and ^{19}F NMR (282 MHz, CDCl_3) spectra were recorded on a Varian Mercury 300 spectrometer using TMS and CCl_3F as internal standards. The reaction progress was controlled by TLC on Silufol UV-254 plates. Chromatographic separation of the products was carried out on a “Puriflash XS 520 Plus” chromatograph using “Kieselgel MN 40-60” silica gel. The eluent was hexane-ethyl acetate (0–20% ethyl acetate) with a gradient increase in polarity.

The general procedure for the synthesis of 1,4-dichloro-2-(difluoromethoxy)-5-nitrobenzene (4) and 1-chloro-2-(difluoromethoxy)-4-fluoro-5-nitrobenzene (5)

Haloaryldifluoromethyl ether **10a** or **10b** (0.1 mol) was added dropwise or in portions to a mixture of 96% sulfuric acid (50 mL) and 100% nitric acid (25 mL), keeping the temperature within the range of 20–30°C. The mixture was stirred at this temperature for 30 min, after which the reaction was quenched by pouring it onto ice. The resulting mixture was extracted with MTBE (2×200 mL), and the combined organic layers were washed with 5% aqueous sodium bicarbonate solution (3×300 mL), followed by water until the washes became colorless. The organic phase was dried over MgSO_4 , the solvent was evaporated,

and the residue was crystallized from hexane by freezing at –18 °C, giving the target products as almost colorless, slightly yellow-tinted, low-melting crystals.

1,4-Dichloro-2-(difluoromethoxy)-5-nitrobenzene (4)

A white solid. Yield – 22.4 g (87%). M. p. 41–42 °C. Anal. Calcd for $\text{C}_7\text{H}_3\text{Cl}_2\text{F}_2\text{NO}_3$, %: C 32.59, H 1.17, N 5.43. Found, %: C 32.48, H 1.11, N 5.57. ^1H NMR (300 MHz, CDCl_3), δ , ppm: 6.65 (1H, t, $^1J_{\text{HF}} = 72$ Hz, O- CHF_2), 7.22 (1H, s, ArH), 8.21 (1H, s, ArH). ^{19}F NMR (282 MHz, CDCl_3), δ , ppm: –84.7 (d, $J = 72$ Hz, O- CHF_2).

1-Chloro-2-(difluoromethoxy)-4-fluoro-5-nitrobenzene (5)

A white solid. Yield – 21.5 g (89%). M. p. 38–39 °C. Anal. Calcd for $\text{C}_7\text{H}_3\text{ClF}_3\text{NO}_3$, %: C 34.81, H 1.25, N 5.80. Found, %: C 34.78, H 1.28, N 5.90. ^1H NMR (300 MHz, CDCl_3), δ , ppm: 6.66 (1H, t, $^1J_{\text{HF}} = 72$ Hz, O- CHF_2), 7.24 (1H, d, $J = 9$ Hz, ArH), 8.21 (7.24 (1H, d, $J = 3$ Hz ArH). ^{19}F NMR (282 MHz, CDCl_3), δ , ppm: –115.2 (1F, d, $^3J_{\text{HF}} = 9$ Hz, ArF), –84.4 (2F, d, $^1J_{\text{HF}} = 72$ Hz, O- CHF_2).

The general procedure for the synthesis of 2-(difluoromethoxy)-4-fluoro-1-nitrobenzene (7) and 1-(difluoromethoxy)-3-fluoro-2-nitrobenzene (9)

A solution of the corresponding nitrophenols **11** or **12** (47.1 g, 0.3 mol) and Bu_4NBr (4 g) in THF (500 mL) was stirred and cooled, followed by the dropwise addition of a solution of KOH (90 g, 1.6 mol) in H_2O (180 mL). Freon-22 was then bubbled through the vigorously stirred mixture at 30–35 °C (with water cooling bath) until the gas absorption stops, accompanied by a noticeable exothermic effect. If TLC monitoring indicated the incomplete conversion of the starting nitrophenol, an additional portion of KOH (30 g) was added, and bubbling of Freon-22 continued until the gas uptake stopped, and the reaction mixture changed color from cherry-red to lemon-yellow. The total reaction time was approximately 4–5 h. After completion, water (300 mL) and hexane (300 mL) were added, and the mixture was extracted by shaking. The organic layer was separated, washed with 10% aqueous NaCl solution (300 mL), dried over anhydrous K_2CO_3 , and concentrated under reduced pressure. The crude products were purified by vacuum distillation.

2-(Difluoromethoxy)-4-fluoro-1-nitrobenzene (7)

A yellow liquid. Yield – 56.4 g (91%). B. p. 88–90°C at 0.5 Torr. Anal. Calcd for $\text{C}_7\text{H}_4\text{F}_3\text{NO}_3$, %: C 40.60, H 1.95, N 6.76. Found, %: C 40.55, H 2.01, N 6.72. ^1H NMR (300 MHz, CDCl_3), δ , ppm:

6.57 (1H, t, $^1J_{\text{HF}} = 72$ Hz, O-CHF₂), 6.90–7.10 (2H, m, ArH), 7.95–8.05 (1H, m, ArH). ¹⁹F NMR (282 MHz, CDCl₃), δ , ppm: -82.3 (2F, d, $^1J_{\text{HF}} = 72$ Hz, O-CHF₂), -102.6 (1F, d, $J = 9$ Hz, ArF).

1-(Difluoromethoxy)-3-fluoro-2-nitrobenzene (9)

A yellow liquid. Yield – 58.8 g (95%). B. p. 85–87 °C at 0.5 Torr. Anal. Calcd for C₇H₄F₃NO₃, %: C 40.60, H 1.95, N 6.76. Found, %: C 40.42, H 2.10, N 6.53. ¹H NMR (300 MHz, CDCl₃), δ , ppm: 6.56 (1H, t, $^1J_{\text{HF}} = 72$ Hz, O-CHF₂), 7.12–7.26 (2H, m, ArH), 7.45–7.55 (1H, m, ArH). ¹⁹F NMR (282 MHz, CDCl₃), δ , ppm: -120.6 (m, 1F, ArF), -82.2 (d, $^1J_{\text{HF}} = 72$ Hz, O-CHF₂).

The general procedure for the aminodehalogenation of halonitrobenzenes 3–9

Compounds **3–9** (0.1 mol) and 25% aqueous ammonia (100 mL) were placed in a Teflon vessel within an autoclave and stirred at the selected temperature for 5 to 16 h, depending on the compound under study. After completion, the reaction mixture was extracted with MTBE (500 mL), washed with water (3×300 mL), and dried over MgSO₄. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography.

Halonitroanilines **14** (CAS 825-41-2), **17** (CAS 6627-34-5), **19** (CAS 1635-61-6), **21** (CAS 2369-11-1), **22** (CAS 59483-54-4), as well as *meta*-phenylenediamines **15** (CAS 5131-58-8), **18** (CAS 89487-54-7) and **24** (CAS 567-63-5) were commercially available products, and their

characteristics corresponded to the known ones. Nitroaniline **13** was described recently [4]; the product we received complied with the described compound.

4-Chloro-5-(difluoromethoxy)-2-nitroaniline (16)

Yellow crystals. Yield – 20.2 g (83%). M. p. 112–114 °C. Anal. Calcd for C₇H₅ClF₂N₂O₃, %: C 35.24, H 2.11, N 11.74. Found, %: C 35.42, H 2.18, N 11.81. ¹H NMR (300 MHz, CDCl₃), δ , ppm: 6.15 (2H, br.s. NH₂), 6.47 (1H, t, $^1J_{\text{HF}} = 72$ Hz, O-CHF₂), 6.95 (1H, s, ArH), 8.02 (1H, s, ArH). ¹⁹F NMR (282 MHz, CDCl₃), δ , ppm: -81.1 (d, $^1J_{\text{HF}} = 72$ Hz, O-CHF₂).

3-(Difluoromethoxy)-4-nitroaniline (20)

Yellow crystals. Yield – 14.0 g (65%). M. p. 122–124 °C. Anal. Calcd for C₇H₆F₂N₂O₃, %: C 41.19, H 2.96, N 13.72. Found, %: C 41.23, H 2.78, N 13.88. ¹H NMR (300 MHz, CDCl₃), δ , ppm: 5.49 (2H, br.s. NH₂), 6.30–6.33 (2H, m, ArH), 6.47 (1H, t, $^1J_{\text{HF}} = 72$ Hz, O-CHF₂), 7.73 (1H, d, $J = 8$ Hz, ArH). ¹⁹F NMR (282 MHz, CDCl₃), δ , ppm: -81.9 (d, $^1J_{\text{HF}} = 72$ Hz, O-CHF₂).

3-(Difluoromethoxy)-2-nitroaniline (23)

Yellow crystals. Yield – 17.5 g (85%). M. p. 52–53 °C. Anal. Calcd for C₇H₆F₂N₂O₃, %: C 41.19, H 2.96, N 13.72. Found, %: C 41.21, H 2.82, N 13.69. ¹H NMR (300 MHz, CDCl₃), δ , ppm: 5.21 (2H, br.s. NH₂), 6.54 (1H, t, $^1J_{\text{HF}} = 72$ Hz, O-CHF₂), 6.56 (1H, d, $J = 7$ Hz, ArH), 6.70 (1H, d, $J = 7$ Hz, ArH), 7.22 (1H, t, $J = 7$ Hz, ArH). ¹⁹F NMR (282 MHz, CDCl₃), δ , ppm: -81.4 (d, $^1J_{\text{HF}} = 72$ Hz, O-CHF₂).

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Information about the authors:

Kirill I. Petko (corresponding author), Ph.D. in Chemistry, Senior Researcher, Organofluorine Compounds Chemistry Department, Institute of Organic Chemistry of the National Academy of Sciences of Ukraine; <https://orcid.org/0000-0002-2522-0128>; e-mail for correspondence: kirpet@ukr.net; tel. +380505949797.

Andrey A. Filatov, Ph.D. in Chemistry, Senior Researcher, Organofluorine Compounds Chemistry Department, Institute of Organic Chemistry of the National Academy of Sciences of Ukraine; Chemist, Enamine Ltd.; <https://orcid.org/0000-0001-7050-8131>.

Oleksandr O. Yurchenko, Ph.D. in Chemistry, Head of the High-pressure Laboratory, Institute of Organic Chemistry of the National Academy of Sciences of Ukraine; <https://orcid.org/0000-0002-5668-8022>.

Oleksandr V. Volokitin, Engineer, High-pressure Laboratory, Institute of Organic Chemistry of the National Academy of Sciences of Ukraine.