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Features of Nitration of Aromatic Aldehydes with the Difluoromethoxy Group

Abstract

Nitration of aromatic aldehydes with difluoromethoxy group results in the partial *ipso*-substitution of the aldehyde group if difluoromethoxy group is located in the *para*-position to the aldehyde group. The presence of a chlorine atom in the *meta*-position to the aldehyde group increases the contribution of the *ipso*-substitution, while the presence of a chlorine atom in the *ortho*-position to the aldehyde group reduces it. The presence of strong donors (alkoxy groups) in the molecule eliminates the contribution of the *ipso*-substitution.

Keywords: difluorometoxybenzaldehydes; nitration; *ipso*-substitutuion

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Особливості нітрування ароматичних альдегідів, які містять дифлуорометокси-групу

Анотація

Нітрування ароматичних альдегідів з дифлуорометокси-групою призводить до часткового *ipso*-заміщення альдегідної групи, якщо дифлуорометокси-група перебуває в *пара*-положенні до альдегідної групи. Наявність атома хлору у *мета*-положенні до альдегідної групи підвищує внесок *ipso*-заміщення, тоді як наявність атома хлору в *орто*-положенні до альдегідної групи зменшує його. Наявність у молекулі потужних донорів (алкокси-груп) нівелює внесок *ipso*-заміщення.

Ключові слова: дифторометоксибензальдегіди; нітрування; *ipso*-заміщення

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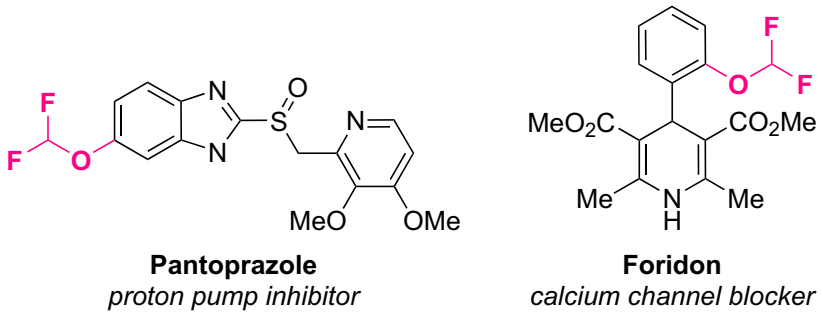
■ Introduction

The difluoromethoxy group has recently become quite readily available, and compounds containing it often exhibit the biological activity [1]. The examples of such prominent $OCHF_2$ bearing drug molecules include a proton pump inhibitor pantoprazole (the brand name Protonix) and a calcium channel blocker riodipine (the brand name Foridon) (**Figure**).

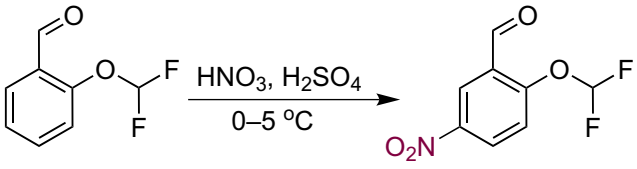
Previously, we obtained a number of biologically active compounds acting as activators of potassium and calcium channels and containing difluoromethoxy group [2]. In particular, starting compounds for our investigations were *o*-difluoromethoxybenzaldehyde (**1**) and its nitration product – 2-difluoromethoxy-5-nitrobenzaldehyde (**2**). Nitration of compound **1** proceeded very easily, even under milder conditions and at lower temperature than nitration of unsubstituted



Pantoprazole
proton pump inhibitor

Foridon
calcium channel blocker

Figure. Examples of bioactive compounds with difluoromethoxy group



1 **2**, *90 %*

Scheme 1. Nitration of *o*-difluoromethoxybenzaldehyde

benzaldehyde, and led to sole product **2** with a high (90%) yield since the substituents in the benzene ring direct nitro group to the same positions (**Scheme 1**).

Nitration of difluoromethoxybenzaldehydes isomeric to **1** and other aromatic aldehydes containing $OCHF_2$ group remained almost unstudied. Only one patent is known on the issue. It describes nitration of *p*-difluorometoxybenzaldehyde in acetic anhydride with a moderate yield [3]. However, such nitration products can become important intermediates for the synthesis of new biologically active substances. This work aims to study the nitration reaction of various benzaldehydes containing difluoromethoxy group, including those with substituent having inconsistent directing influence.

■ Results and discussion

Nitration reactions of aldehydes with the diflouromethoxy group were carried out under conditions close to those of compound **1**, according to the procedure described earlier [2] in a mixture of 96% sulfuric and 100% nitric acids in the ratio of 2:1. We chose *p*-difluorometoxybenzaldehyde (**3**) as the first object of our study. The difluoromethoxy group is a first type director. It activates the *para*-position for electrophilic attacks to a much greater extent than the *ortho*-position. As it was shown earlier, nitration of phenyldifluoromethyl ether under mild conditions leads to the mixture of *p*-nitrophenyldifluoromethyl ether and *o*-nitrophenyldifluoromethyl ether in the ratio of 7:1 [4]. On the other hand, aldehyde group in nitration reactions partially directs the reaction to the *ortho*-position (but never to the *para*-position). Therefore, the described fact that nitration of compound **3** occurred only in the *ortho*-position to the difluoromethoxy group and led to only one product [3] caused us doubt. Nitration at 0–5 °C resulted in a mixture of compounds with the total yield of about 80%. The expected 3-nitro-4-difluoromethoxybenzaldehyde (**4**) was the main reaction product, but the side product was 2,4-dinitrophenyldifluoromethyl ether (**5**). The product of the *ipso*-substitution of aldehyde group **5** was isolated with the aid of chromatography. Compound **5** synthesized according to the method [4] did not give depression of the melting point of the mixed sample with the product obtained according to **Scheme 2**. The ratio of compounds **4** and **5** was 10:1. When carrying out nitration at a higher temperature (15–20°C), a similar mixture was obtained, but with a higher content of the *ipso*-substitution product. The ratio of **4** and **5** in this case was 4:1 (**Scheme 2**).

Previously, only a limited number of cases of the *ipso*-substitution of aldehyde group during nitration of aromatic aldehydes were known. Such a substitution could occur only if the CHO group was in the *para*-position to the alkoxy substituent (OR), and possibly passed through the oxonium intermediate **6** (**Scheme 3**). The content of *ipso*-substitution products in the reaction mixture increased with an increase of the reaction temperature. Thus, nitration of anisaldehyde at 0 °C led only to 3-nitro-4-methoxybenzaldehyde and did not provide an admixture of the *ipso*-substitution product [5], while nitration of anisaldehyde

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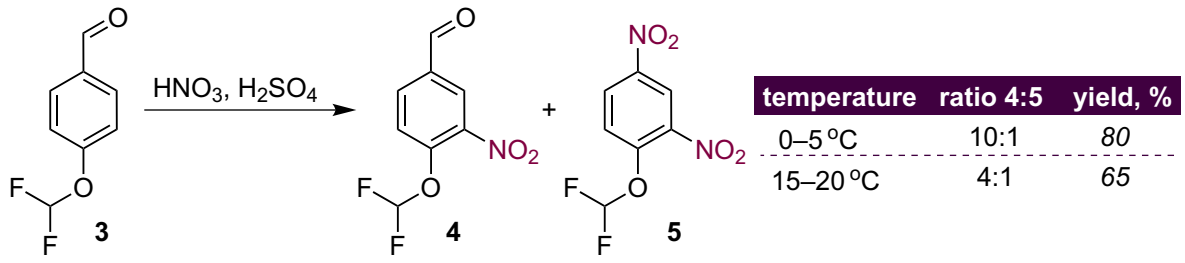
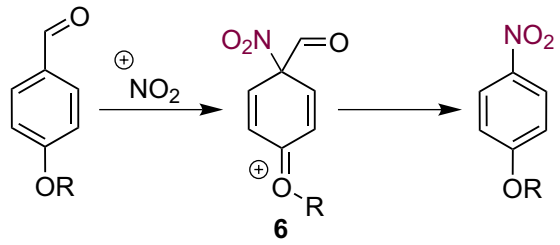


temperature	ratio 4:5	yield, %
0–5 °C	10:1	*80*
15–20 °C	4:1	*65*

Scheme 2. Nitration of *p*-difluoromethoxybenzaldehyde

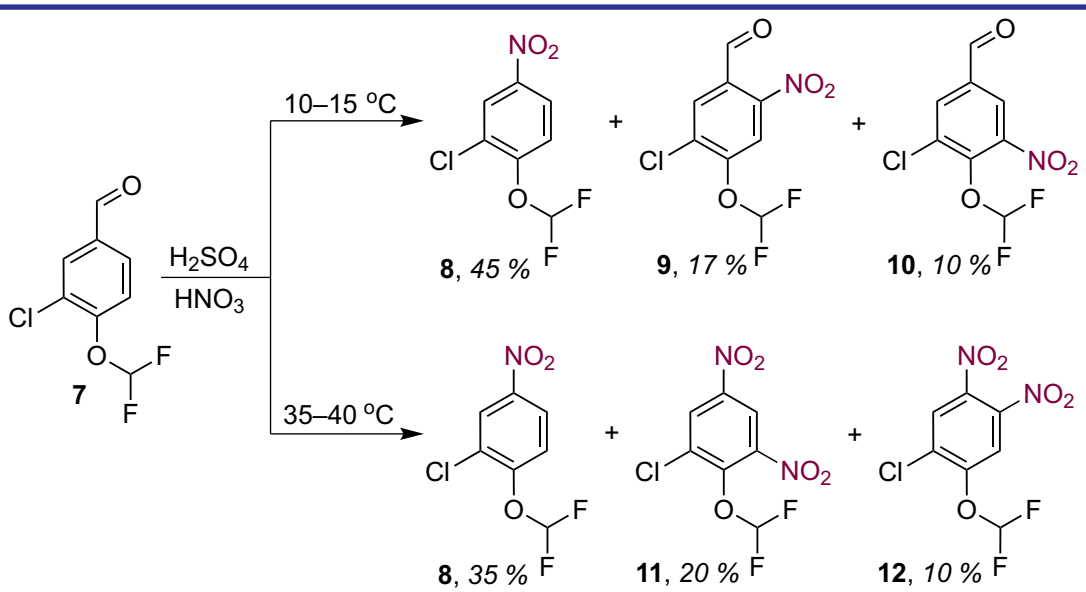


Scheme 3. The possible pathway of the *ipso*-substitutution

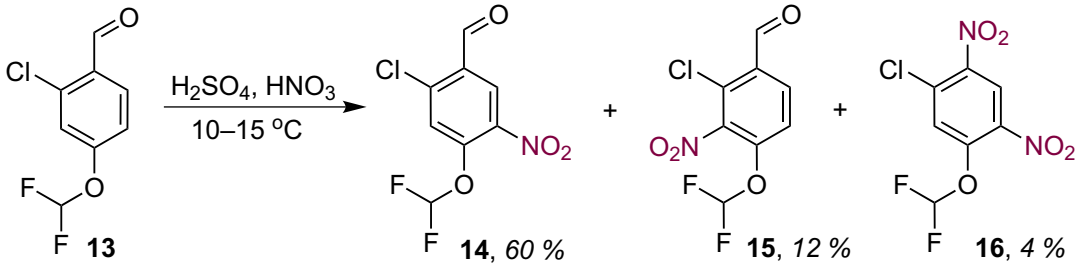
with bismuth nitrate at 80 °C resulted in a mixture of two products containing 30% of *p*-nitroanisole [6]. If nitration to the *ortho*-position of the OR substituent is sterically restricted and the reaction is directed to the *ortho*-position of the aldehyde group, then the content of the *ipso*-substitution product also increases. So, to obtain 6-nitrovaniline, the nitration reaction of *O*-benzylvanillin was used. In this case, even when using mild conditions at least 20% of the *ipso*-substitution product was formed [7].

We studied nitration of other aromatic aldehydes with a difluoromethoxy group in the *para*-position under similar conditions. It turned out that the presence of a chlorine atom in the *meta*-position to the aldehyde group complicated the nitration reaction (the reaction did not proceed at 0 °C) and led to a sharp increase in the content of *ipso*-substitution products. Thus, during nitration of 3-chloro-4-difluoromethoxybenzaldehyde (**7**) at 10–15 °C, the main reaction product was 2-chloro-4-nitrophenyldifluoromethyl ether (**8**) isolated in 45% yield, and the yields of nitroaldehydes **9** and **10** were 17 and 10%, respectively (**Scheme 4**). Compound **8** was described earlier [8], and the product we obtained corresponded to that. The structure of compounds **9** and **10** was unambiguously proven by ^{1}H NMR spectra. Thus, in the case of compound **9**, the signals of the benzene ring protons appear as narrow singlets, which indicates their *para*-arrangement. In the case of compound **10**, the signals of two protons of the benzene ring appear as two doublets with a small spin-spin coupling constant of about 1 Hz, which corresponds to the *meta*-position of the protons.

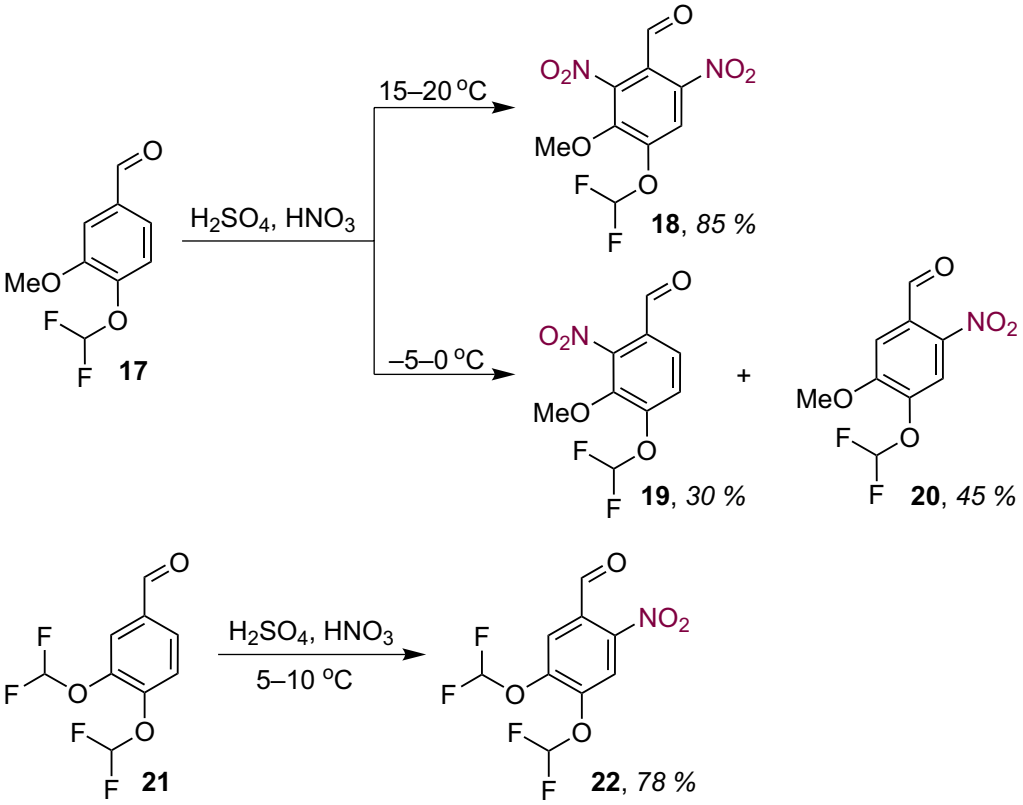
When carrying out nitration at a higher temperature (35–40 °C), aldehydes were not found among the reaction products. A mixture of nitro product **8** and dinitro compounds **11** and **12** were obtained in about 65% overall yield. The structure of compounds **11** and **12** was confirmed similarly to compounds **9** and **10**. The signals of the benzene ring protons in compound **11** appear as



Scheme 4. Nitration of 3-chloro-4-difluoromethoxybenzaldehyde



Scheme 5. Nitration of 2-chloro-4-difluoromethoxybenzaldehyde



Scheme 6. Nitration of *O*-difluoromethylvanillin and 3,4-*bis*(difluoromethoxy)benzaldehyde

two doublets with a small spin-spin coupling constant (about 1 Hz), while in the case of compound **12**, the signals of the benzene ring protons appear as narrow singlets. In compound **12**, two nitro groups are in the *ortho*-position to each other, which is not typical for dinitration products. Nitration of compound **8** leads almost unequivocally to compound **11**, the second nitro group is directed to the *meta*-position relative to the first one. Thus, the formation of compound **12** most likely occurs as a result of the *ipso*-substitution of the aldehyde group in compound **9**.

On the contrary, the presence of a chlorine atom in the *ortho*-position to aldehyde group significantly hinders the formation of *ipso*-substitution products. Thus, we studied nitration of 2-chloro-4-difluoromethoxybenzaldehyde (**13**) (**Scheme 5**). As in the case of aldehyde **7**, the reaction did not proceed at 0 °C; however, at 10–15 °C, nitration led to the formation of a mixture of two aldehydes **14** and **15** in the ratio of 5:1 with a total yield of about 75%, and only an insignificant (2–4%) impurity of the *ipso*-substitution product **16**. Aldehyde **14** was isolated from the reaction mixture by crystallization in about 50% yield. Carrying out the nitration at 20–25 °C resulted in a slight increase in the yield of product **16**, up to 7–9%. Obviously, the decrease in the amount of *ipso*-substitution products is due to steric hindrance created by the chlorine atom, complicating the formation of the intermediate compound type **6**.

The introduction of electron donating methoxy group into the molecule greatly facilitates the nitration reaction and completely excludes the formation of *ipso*-substitution products during nitration under the conditions studied (**Scheme 6**). Thus, during nitration of *O*-difluoromethylvanillin (**17**), two nitro groups were partially introduced into the molecule already at 0–5 °C and during nitration at 5–10 °C *di*nitro compound **18**

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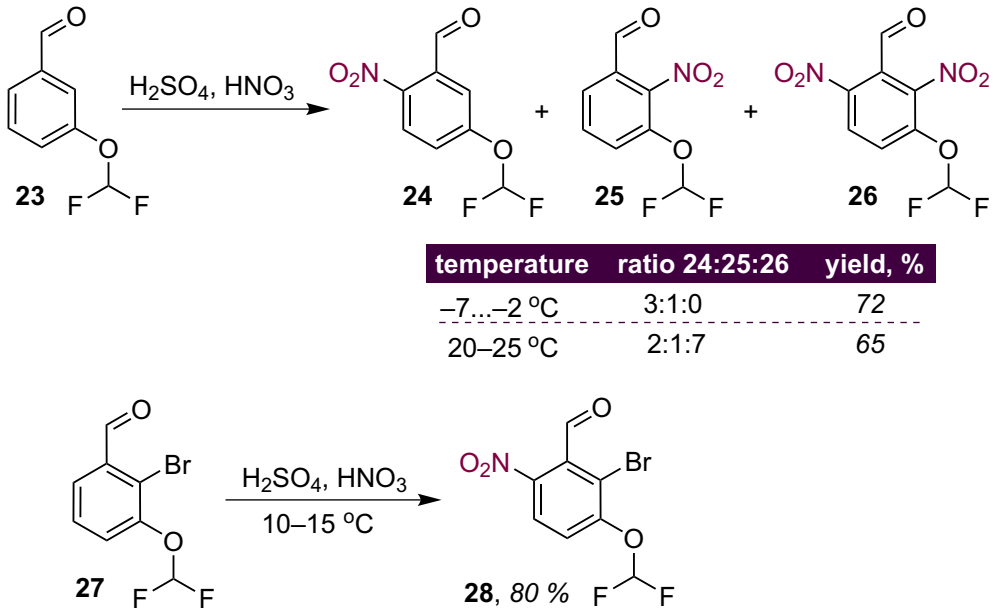

temperature	ratio 24:25:26	yield, %
–7...–2 °C	3:1:0	*72*
20–25 °C	2:1:7	*65*

Scheme 7. Nitration of *m*-difluoromethoxybenzaldehyde and 2-bromo-3-difluoromethoxybenzaldehyde

became the main reaction product. At the same time nitration of compound **17** at 15–20 °C led to the formation of only 2,6-*di*nitro-*O*-difluoromethylvanillin (**18**) in a high yield (**Scheme 6**). Carrying out the reaction at a temperature not exceeding 0 °C, with the gradual addition of an equimolar amount of nitric acid, led to the production of two *mono*nitro products – 2-nitro-*O*-difluoromethylvanillin (**19**) and 6-nitro-*O*-difluoromethylvanillin (**20**) in the ratio of 2:3 and the total yield of 75%. Activation of the *ortho*- and *para*-positions by a strong donor completely determined the direction of the reaction. Nitration of 3,4-*bis*(difluoromethoxy)benzaldehyde (**21**) at 5–10 °C was not accompanied by the formation of *ipso*-substitution products as well and proceeded with the formation of only one product – 3,4-*bis*(difluoromethoxy)-6-nitrobenzaldehyde (**22**) since the difluoromoxy group mostly activates the *para*-position.

Nitration of *m*-difluoromethoxybenzaldehyde (**23**) under the studied conditions proceeded at temperatures below 0 °C and led to a mixture of isomers **24** and **25**. Meanwhile, nitration at 20–25 °C provided a significant admixture of the *di*nitro product **26**. The introduction of a bromine atom into position 2 of *m*-difluoromethoxybenzaldehyde made nitration somewhat difficult (the reaction did not proceed at 0 °C), but led to the formation of only single product. Thus, nitration of 2-bromo-3-difluoromethoxybenzaldehyde (**27**) resulted in one nitration product **28**. The structure of compound **28** was unambiguously proven by ^{1}H NMR experiments since proton signals of the aromatic nucleus appeared as two doublets with a spin-spin interaction constant of about 10 Hz corresponding to the *ortho*-position of protons.

In all cases of nitration of *m*-difluoromethoxybenzaldehydes, no signs of *ipso*-substitution were found.

■ Conclusion

In summary, the features of nitration of aromatic aldehydes containing difluoromethyl group have been studied. Some relationships have been found between the structure of the molecule, the reaction conditions, and the contribution of the *ipso*-substitution products of the aldehyde group.

■ Experimental part

Melting points were measured in an open capillary and given uncorrected. ^{1}H NMR (300 MHz, $CDCl_3$), ^{13}C NMR (75 MHz, $CDCl_3$), and ^{19}F NMR (288 MHz, $CDCl_3$) 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. The chromatographic separation of products was carried out on a "Puriflash XS 520 Plus" chromatograph using a "Kieselgel MN 40-60" silica gel. The eluent was hexane/ethyl acetate (0-20% ethyl acetate) with a gradient increase in polarity.

p-Difluorometoxybenzaldehyde (**3**) [9], *O*-difluorometoxyvaniline (**17**) [3], 3,4-*bis*(difluoromethoxy)-benzaldehyde (**21**) [10], and *m*-difluoromethoxybenzaldehide (**23**) [11] were obtained according to the literature procedures.

3-Chloro-4-difluoromethoxybenzaldehyde (7), 2-chloro-4-difluometoxy-benzaldehyde (13) and 2-bromo-3-difluorometoxybenzaldehyde (27). The general procedure of difluoromethylation of corresponding hydroxybenzaldehydes

A solution of a corresponding hydroxybenzaldehyde (0.3 mol) in dioxane (200 mL) was stirred and treated by adding a solution of KOH (90 g, 1.5 mol) in H_2O (180 mL). Freon-22 was bubbled through the vigorously stirred reaction mixture at 45–55 °C until the absorption of gas ceased (the exothermic effect was observed). The reaction was monitored by TLC. If a starting hydroxybenzaldehyde remained, an additional KOH (30 g) was added, and Freon-22 was bubbled until the absorption of gas ceased. The reaction overall time was about 4–5 h. Water (300 mL) was added, the product was extracted by shaking with MTBE (2×300 mL), the organic layer was separated and washed with water (3×300 mL), dried over anhydrous K_2CO_3, and the solvent was evaporated at a reduced pressure. The product was purified by fractional distillation *in vacuo* (**7**, **13**) or crystallization from hexane (**27**).

3-Chloro-4-difluoromethoxybenzaldehyde (**7**)

A colorless liquid. Yield – 78%. B. p. 74–76 °C/0.5 Torr. Anal. Calcd for $C_8H_5ClF_2O_2$, %: C 46.51; H 2.44; Cl 17.16. Found, %: C 46.55; H 2.51; Cl 17.32. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.64 (1H, t, J = 72.0 Hz, O-CHF_2); 7.36 (1H, d, J = 7.0 Hz, ArH); 7.76 (1H, dd, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.0 Hz, ArH); 7.92 (1H, J = 1.0 Hz, ArH); 9.89 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 115.2 (t, J = 287.0 Hz, O-CHF_2); 120.4; 126.9; 129.5; 131.5; 134.0; 151.1; 189.6. ^{19}F NMR (288 MHz, $CDCl_3$), δ, ppm: -82.7 (d, J = 72.0 Hz, O-CHF_2).

2-Chloro-4-difluoromethoxybenzaldehyde (**13**)

A colorless liquid. Yield – 72%. B. p. 76–78 °C/0.5 Torr. Anal. Calcd for $C_8H_5ClF_2O_2$, %: C 46.51; H 2.44; Cl 17.16. Found, %: C 46.71; H 2.52; Cl 17.27. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.65 (1H, t, J = 72.0 Hz, O-CHF_2); 7.12 (1H, dd, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.0 Hz, ArH); 7.27 (1H, J = 1.0 Hz, ArH); 7.97 (1H, d, J = 7.0 Hz, ArH); 10.44 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 115.5 (t, J = 287.0 Hz, O-CHF_2); 120.4; 126.7; 126.9; 128.5; 135.5; 148.4; 191.1. ^{19}F NMR (288 MHz, $CDCl_3$), δ, ppm: -81.4 (d, J = 72.0 Hz, O-CHF_2).

2-Bromo-3-difluorometoxybenzaldehyde (**27**)

A white solid. Yield – 83%. M. p. 63–64 °C. Anal. Calcd for $C_8H_5BrF_2O_2$, %: C 38.28; H 2.01; Br 31.83. Found, %: C 38.48; H 2.11; Br 32.07. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.58 (1H, t, J = 72.0 Hz, O-CHF_2); 7.43–7.48 (2H, m, ArH); 7.77–7.87 (1H, m, ArH); 10.38 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 108.9 (C-Br); 115.5 (t, J = 287.0 Hz, O-CHF_2); 121.4; 125.7; 128.5; 132.5; 143.9; 187.9. ^{19}F NMR (288 MHz, $CDCl_3$), δ, ppm: -81.1 (d, J = 72.0 Hz, O-CHF_2).

The general procedure for nitration of aldehydes 3, 7, 13, 17, 21, and 27

An aldehyde (0.02 mol) was added dropwise or in portions to a mixture of 96% sulfuric acid (10 mL) and 100% nitric acid (5 mL) in such a rate that the temperature did not exceed the initially selected temperature by more than 5 °C. After stirring at this temperature for 30 minutes, the reaction mixture was poured onto ice. The product was extracted with MTBE (2×100 mL), washed with a 5% aq soda solution (2×100 mL), the solvent was evaporated off, and the residue was crystallized from hexane in the case of compounds **14**, **18**, and **28**, or distilled in a vacuum in the case of compound **22**. In other cases, the mixture was separated chromatographically. To obtain compounds **19** and **20** nitric acid (1.5 g, 0.022 mol) was added dropwise to the stirred suspension of *O*-difluorometoxyvaniline (**17**) (4.05 g, 0.02 mol) in 10 mL of 96% sulfuric acid.

3-Nitro-4-difluoromethoxybenzaldehyde (**4**)

A yellow solid. Yield – 50–72%. M. p. 33–35 °C (Lit. [3] – oil). Anal. Calcd for $C_8H_5F_2NO_4$, %: C 44.24; H 2.32; N 6.45. Found, %: C 44.55; H 2.28; N 6.42. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.71 (1H, t, J = 72.0 Hz, O-CHF_2); 7.55 (1H, d, J = 7.0 Hz, ArH); 8.12 (1H, dd, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.0 Hz, ArH); 8.33 (1H, J = 1.0 Hz, ArH); 10.05 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 115.2 (t, J = 287.0 Hz, O-CHF_2); 122.4; 133.6; 134.5; 142.5; 147.3; 150.1; 188.6. ^{19}F NMR (288 MHz, $CDCl_3$), δ, ppm: -84.5 (d, J = 72.0 Hz, O-CHF_2).

5-Chloro-4-difluoromethoxy-2-nitrobenzaldehyde (**9**)

A yellow solid. Yield – 17%. M. p. 54–55 °C. Anal. Calcd for $C_8H_4ClF_2NO_4$, %: C 38.20; H 1.60; N 5.57. Found, %: C 38.35; H 1.78; N 5.42. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.78 (1H, t, J = 72.0 Hz, O-CHF_2); 8.02 (1H, s, ArH); 8.04 (1H, s, ArH); 10.36 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 114.5 (t, J = 287.0 Hz, O-CHF_2); 115.4; 128.6; 131.7; 132.8; 147.9; 149.5; 185.6. ^{19}F NMR (288 MHz, $CDCl_3$), δ, ppm: -83.2 (d, J = 72.0 Hz, O-CHF_2).

5-Chloro-4-difluoromethoxy-3-nitrobenzaldehyde (**10**)

A yellow oil. Yield – 10%. Anal. Calcd for $C_8H_4ClF_2NO_4$, %: C 38.20; H 1.60; N 5.57. Found, %: C 38.37; H 1.68; N 5.66. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.74 (1H, t, J = 72.0 Hz, O-CHF_2); 8.25 (1H, d, J = 1.0 Hz, ArH); 8.31 (1H, d, J = 1.0 Hz,

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ArH); 10.01 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 114.8 (t, J = 287.0 Hz, O-CHF_2); 124.4; 133.1; 134.7; 143.4; 146.0; 149.1; 187.4. ^{19}F NMR (288 MHz, $CDCl_3$), δ, ppm: -81.7 (d, J = 72.0 Hz, O-CHF_2).

2-Chloro-4,6-dinitrophenyldifluoromethyl ether (**11**)

A yellow oil. Yield – 20%. Anal. Calcd for $C_7H_3ClF_2N_2O_5$, %: C 31.31; H 1.13; N 10.43. Found, %: C 31.36; H 1.21; N 10.42. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.77 (1H, t, J = 72.0 Hz, O-CHF_2); 8.60 (1H, d, J = 1.0 Hz, ArH); 8.69 (1H, d, J = 1.0 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 115.4 (t, J = 287.0 Hz, O-CHF_2); 118.9; 129.4; 133.5; 143.9; 144.8; 145.1. ^{19}F NMR (288 MHz, $CDCl_3$), δ, ppm: -85.7 (d, J = 72.0 Hz, O-CHF_2).

2-Chloro-4,5-dinitrophenyldifluoromethyl ether (**12**)

A yellow oil. Yield – 10%. Anal. Calcd for $C_7H_3ClF_2N_2O_5$, %: C 31.31; H 1.13; N 10.43. Found, %: C 31.42; H 1.17; N 10.53. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.75 (1H, t, J = 72.0 Hz, O-CHF_2); 7.82 (1H, s, ArH); 8.07 (1H, s, ArH). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 114.4 (t, J = 287.0 Hz, O-CHF_2); 116.5; 123.1; 127.7; 140.4; 144.0; 147.1. ^{19}F NMR (288 MHz, $CDCl_3$), δ, ppm: -82.8 (d, J = 72.0 Hz, O-CHF_2).

2-Cloro-4-difluoromethoxy-5-nitrobenzaldehyde (**14**)

A yellow solid. Yield – 60%. M. p. 60–61 °C. Anal. Calcd for $C_8H_4ClF_2NO_4$, %: C 38.20; H 1.60; N 5.57. Found, %: C 38.37; H 1.68; N 5.66. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.70 (1H, t, J = 72.0 Hz, O-CHF_2); 8.25 (1H, s, ArH); 8.31 (1H, s, ArH); 10.37 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 114.9 (t, J = 287.0 Hz, O-CHF_2); 124.0; 126.6; 129.9; 141.1; 142.2; 146.7; 186.2. ^{19}F NMR (288 MHz, $CDCl_3$), δ, ppm: -83.1 (d, J = 72.0 Hz, O-CHF_2).

2-Chloro-4-difluoromethoxy-3-nitrobenzaldehyde (**15**)

A yellow solid. Yield – 12%. M. p. 49–50 °C. Anal. Calcd for $C_8H_4ClF_2NO_4$, %: C 38.20; H 1.60; N 5.57. Found, %: C 38.42; H 1.72; N 5.71. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.57 (1H, t, J = 72.0 Hz, O-CHF_2); 7.47 (1H, d, J = 7.0 Hz, ArH); 8.02 (1H, d, J = 7.0 Hz, ArH); 10.39 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 114.7 (t, J = 287.0 Hz, O-CHF_2); 118.3; 126.6; 129.9; 131.5; 141.2; 142.5; 186.3. ^{19}F NMR (288 MHz, $CDCl_3$), δ, ppm: -84.4 (d, J = 72.0 Hz, O-CHF_2).

3-Chloro-4,6-dinitrophenyldifluoromethyl ether (**16**)

A yellow oil. Yield – 4%. Anal. Calcd for $C_7H_3ClF_2N_2O_5$, %: C 31.31; H 1.13; N 10.43. Found, %: C 31.42; H 1.17; N 10.54. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.76 (1H, t, J = 72.0 Hz, O-CHF_2); 7.67 (1H, s, ArH); 8.61 (1H, s, ArH). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 114.8 (t, J = 287.0 Hz, O-CHF_2); 123.6; 124.5; 133.5; 140.0; 143.8; 145.5. ^{19}F NMR (288 MHz, $CDCl_3$), δ, ppm: -86.9 (d, J = 72.0 Hz, O-CHF_2).

2,6-Dinitro-O-difluoromethylvanillin (**18**)

A white solid. Yield – 85%. M. p. 58–59 °C. Anal. Calcd for $C_9H_6F_2N_2O_7$, %: C 37.00; H 2.07; N 9.59. Found, %: C 36.85; H 2.12; N 9.72. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 4.14 (3H, s, OCH_3); 6. 76 (1H, t, J = 72.0 Hz, O-CHF_2); 8.20 (1H, s, ArH); 10.25 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 63.5 (OCH_3); 115.2 (t, J = 287.0 Hz, O-CHF_2); 118.9; 124.7; 142.0; 144.1; 145.7; 148.8; 183.8. ^{19}F NMR (288 MHz, $CDCl_3$), δ, ppm: -82.2 (d, J = 72.0 Hz, O-CHF_2).

2-Nitro-O-difluoromethylvanillin (**19**)

A white solid. Yield – 30%. M. p. 61–62 °C. Anal. Calcd for $C_9H_7F_2N_2O_5$, %: C 43.74; H 2.85; N 5.67. Found, %: C 43.65; H 2.72; N 5.72. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 4.00 (3H, s, OCH_3); 6.72 (1H, t, J = 72.0 Hz, O-CHF_2); 7.48 (1H, d, J = 7.0 Hz, ArH); 7.71 (1H, d, J = 7.0 Hz, ArH); 9.89 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 63.2 (OCH_3); 115.2 (t, J = 287.0 Hz, O-CHF_2); 118.9; 121.6; 124.5; 127.2; 142.2; 149.4; 185.7. ^{19}F NMR (288 MHz, $CDCl_3$), δ, ppm: -82.1 (d, J = 72.0 Hz, O-CHF_2).

6-Nitro-O-difluoromethylvanillin (**20**)

A white solid. Yield – 45%. M. p. 75–76 °C. Anal. Calcd for $C_9H_7F_2N_2O_5$, %: C 43.74; H 2.85; N 5.67. Found, %: C 43.87; H 2.76; N 5.60. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 4.04 (3H, s, OCH_3); 6.70 (1H, t, J = 72.0 Hz, O-CHF_2); 7.46 (1H, 1H, s, ArH); 7.98 (1H, s, ArH); 10.44 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 59.5 (OCH_3); 111.3; 115.2 (t, J = 287.0 Hz, O-CHF_2); 128.5; 124.5; 130.4; 142.4; 155.5; 187.4. ^{19}F NMR (288 MHz, $CDCl_3$), δ, ppm: -82.4 (d, J = 72.0 Hz, O-CHF_2).

3,4-Bis(difluoromethoxy)-6-nitrobenzaldehyde (**22**)

A yellow oil. Yield – 78%. B. p. 112–114 °C/ 0.5 Torr. Anal. Calcd for $C_9H_5F_4NO_5$, %: C 38.18; H 1.78; N 4.95. Found, %: C 38.37; H 2.06; N 5.02. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.71 (1H, t, J = 72.0 Hz, O-CHF_2); 7.80 (1H, s, ArH); 8.05 (1H, s, ArH); 10.37 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 114.9 (t, J = 287.0 Hz, O-CHF_2); 115.2 (t, J = 287.0 Hz, O-CHF_2); 118.3; 120.7; 144.5; 145.9; 146.1; 186.1. ^{19}F NMR (288 MHz, $CDCl_3$), δ, ppm: -82.4 (d, J = 72.0 Hz, O-CHF_2).

2-Nitro-5-difluoromethoxybenzaldehyde (**24**)

A white solid. Yield – 25-45%. M. p. 35–37 °C. Anal. Calcd for $C_8H_5F_2NO_4$, %: C 44.24; H 2.32; N 6.45. Found, %: C 44.33; H 2.29; N 6.49. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.69 (1H, t, J = 72.0 Hz, O-CHF_2); 7.85 (1H, d, J = 1.0 Hz,

ArH); 7.90 (1H, d, J = 7.0 Hz, ArH); 8.04 (1H, dd, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$= 1.0 Hz, ArH); 10.09 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 115.2 (t, J = 287.0 Hz, O-CHF_2); 122.9; 126.2; 127.2; 139.6; 143.3; 145.9; 189.1. ^{19}F NMR (288 MHz, $CDCl_3$), δ, ppm: -82.7 (d, J = 72.0 Hz, O-CHF_2).

2-Nitro-3-difluoromethoxybenzaldehyde (**25**)

A white solid. Yield – 12-20%. M. p. 25–27 °C. Anal. Calcd for $C_8H_5F_2NO_4$, %: C 44.24; H 2.32; N 6.45. Found, %: C 44.29; H 2.42; N 6.54. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.61 (1H, t, J = 72.0 Hz, O-CHF_2); 7.65 (1H, d, J = 7.0 Hz, ArH); 7.75 (1H, t, J = 7.0 Hz, ArH); 7.84 (1H, d, J = 7.0 Hz, ArH); 9.94 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 115.2 (t, J = 287.0 Hz, O-CHF_2); 123.0; 126.8; 127.9; 128.5; 132.0; 142.4; 186.2. ^{19}F NMR (288 MHz, $CDCl_3$), δ, ppm: -82.0 (d, J = 72.0 Hz, O-CHF_2).

2,6-Dinitro-5-difluoromethoxybenzaldehyde (**26**)

A white solid. Yield – 0-50%. M. p. 57–58 °C. Anal. Calcd for $C_8H_4F_2N_2O_6$, %: C 36.66; H 1.54; N 10.69. Found, %: C 36.56; H 1.42; N 10.46. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.71 (1H, t, J = 72.0 Hz, O-CHF_2); 7.69 (1H, d, J = 7.0 Hz, ArH); 8.39 (1H, d, J = 7.0 Hz, ArH); 10.24 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 114.7 (t, J = 287.0 Hz, O-CHF_2); 122.7; 127.6; 128.8; 140.7; 143.0; 146.0; 183.7. ^{19}F NMR (288 MHz, $CDCl_3$), δ, ppm: -83.2 (d, J = 72.0 Hz, O-CHF_2).

2-Bromo-3-difluoromethoxy-6-nitrobenzaldehyde (**28**)

A white solid. Yield – 80%. M. p. 63–64 °C. Anal. Calcd for $C_8H_4BrF_2NO_4$, %: C 32.46; H 1.36; Br 26.99. Found, %: C 32.55; H 1.21; Br 27.07. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 6.71 (1H, t, J = 72.0 Hz, O-CHF_2); 7.45 (1H, d, J = 7.0 Hz, ArH); 8.11 (1H, d, J = 7.0 Hz, ArH); 10.20 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 107.3 (C-Br); 114.4 (t, J = 287.0 Hz, O-CHF_2); 120.8; 125.0; 136.4; 143.8; 152.4; 187.0. ^{19}F NMR (288 MHz, $CDCl_3$), δ, ppm: -83.3 (d, J = 72.0 Hz, O-CHF_2).

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