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Introduction of the Difluoro(methoxy)methyl Group into the Aromatic Ring and the Study of Its Electronic Properties

Abstract

A simple and efficient method for synthesizing aromatic compounds with a difluoro(methoxy)methyl fragment (CF_2OCH_3) by the fluorodesulfurization of thionoesters has been developed. Systematic screening identified $SnCl_4$/DAST as the optimal reagent combination, providing excellent selectivity and high yields of target products. A series of aromatic difluoro(methoxy)methyl compounds was synthesized under these conditions. Further studies of the electronic properties of the difluoro(methoxy)-methyl group using ^{19}F NMR allowed us to determine its Hammett constants for inductive (σ_I) and resonance (σ_R) effects. The results show that CF_2OCH_3 acts as a moderately electron-withdrawing substituent, underscoring its potential as a versatile group for designing organic molecules with precisely tuned electronic characteristics.

Keywords: difluoro(methoxy)methyl; fluorodesulfurization; Hammett constants

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Введення дифторо(метокси)метильної групи в ароматичне кільце та дослідження її електронних властивостей

Анотація

Розроблено простий та ефективний метод синтезу ароматичних сполук із дифторо(метокси)метильним фрагментом (CF_2OCH_3) шляхом фтородесульфуризації тіонових естерів. Під час систематичного пошуку умов реакції було визначено, що оптимальним поєднанням реагентів є $SnCl_4$/DAST, яке забезпечує відмінну селективність процесу та високі виходи цільових продуктів. З використанням цих умов було синтезовано серію ароматичних дифторо(метокси)метильних похідних. Подальше дослідження електронних властивостей дифторо(метокси)метильної групи за допомогою ^{19}F ЯМР дозволило визначити її константи Гаммета для індуктивного (σ_I) та резонансного (σ_R) ефектів. Отримані результати свідчать, що дифторо(метокси)метильна група є помірно електроноакцепторним замісником, що робить її цікавим структурним фрагментом для побудови органічних молекул із необхідними електронними характеристиками.

Ключові слова: дифторо(метокси)метил; фтородесульфуризація; константи Гаммета

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■ Introduction

The development of methodologies for introducing difluoro(alkoxy)methyl fragments (CF_2OR) into organic molecules has gained prominence in the chemical community, owing to their distinctive impact on the physicochemical and biological properties of compounds [1, 2]. In particular, the difluoro(methoxy)methyl group (CF_2OCH_3) combines the electron-withdrawing properties of a CF_2 moiety with the ambiguous electronic nature of a methoxy substituent, potentially resulting in an intriguing balance of field (inductive) and resonance effects.

Traditionally, the synthesis of difluoro(alkoxy)-methyl ethers has relied on aggressive reagents, such as SF_4 [3], BrF_3 [4], or HF with oxidant systems [5], which typically demand elevated temperatures and pressures, and often involve toxic or explosive conditions. More moderate protocols employing DAST and related reagents [6] can enable the fluorodesulfurization under milder conditions, but they may be limited by compatibility issues with certain functional groups. Recent literature has described the use of silver(I) salts (AgF) [7] for similar transformations although this approach is quite sensitive to the purity of the AgF reagent.

Despite progress in the synthesis of difluoro(alkoxy)methyl compounds, the electronic properties of the CF_2OCH_3 group, particularly in terms of its Hammett constants, have remained largely unexplored. The first objective of our study, therefore, was to develop a convenient method for accessing aryl-CF_2OCH_3 derivatives by utilizing thionoesters as precursors to install the difluoro(methoxy)-methyl group. The second goal was to study the electronic characteristics of the CF_2OCH_3 group and determine its Hammett constants (σ_I and σ_R) comparing these values with those of related fluorinated substituents [8]. The Hammett analysis was performed *via* the ^{19}F NMR approach [9, 10, 13].

■ Results and discussion

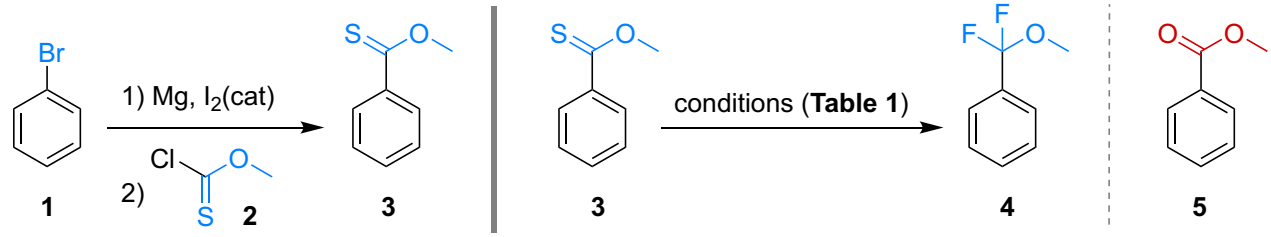
Optimization of the aryl-CF_2OCH_3 synthesis

We selected *O*-methyl benzothioate (**3**) as a model substrate to evaluate the transformation of a methyl thionoester into a difluoro(methoxy)methyl group. Thionoesters were prepared from the corresponding aryl bromides using *O*-methyl carbonochloridothioate (**2**), following a reported procedure [11]. According to the literature, there are three main strategies for converting thionoesters into difluoro-(alkoxy)methyl compounds: (1) using DAST or related fluorinating reagents [6]; (2) using oxidizing agents for the fluorination [5, 12]; (3) performing the nucleophilic fluorine substitution with *S*-selective metal fluorides (or their salts) in the presence of additional fluoride sources [7]. It is important to note that methods not relying on DAST or morphDAST were very sensitive to the presence of water; in many experiments, methyl benzoate (**5**) appeared as an impurity or even the main product. After testing various conditions for forming the difluoro(methoxy)-methyl group, we found that the best results came from using DAST with small (catalytic) amounts of tin chlorides ($SnCl_2$ or $SnCl_4$). This approach, in our opinion, is the most effective since it tolerates trace moisture and uses readily available reagents.

Using the $SnCl_4$/DAST method to convert methyl thionoesters into difluoro(methoxy)methyl derivatives, we synthesized a series of aromatic compounds **4a–l** containing the CF_2OCH_3 group (**Figure 1**).

Determination of Hammett Constants

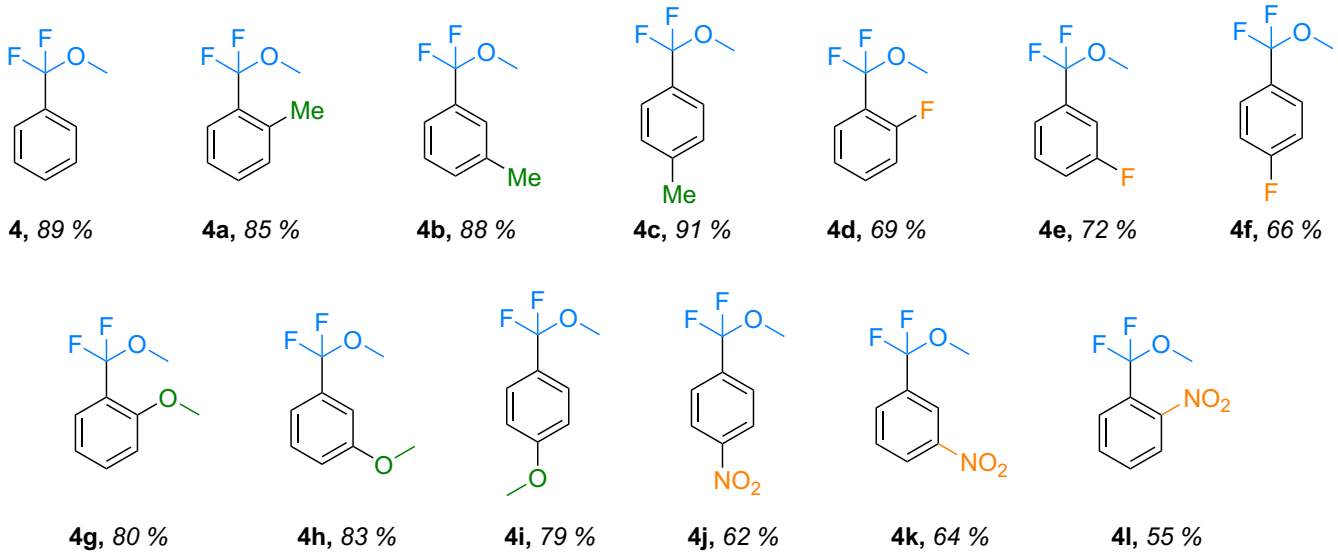
Compounds **4e** and **4f** were used to measure Hammett constants *via* the ^{19}F NMR method. This method is known to be simple and often used for studying electronic properties [13]. The ^{19}F NMR spectra were recorded in the presence of small amounts of hexafluorobenzene (to calibrate chemical shifts) and monofluorobenzene. From the difference in ^{19}F chemical shifts between monofluorobenzene



Scheme 1. The synthetic approach to the synthesis of difluoro(methoxy)methyl compounds

Table 1. Screening fluorination conditions for forming the difluoro(methoxy)-methyl group

Reagents	Conditions	Result
morpDAST 2 equiv.	DCM, rt, 16 h	No reaction
$SbCl_3$ 0.05 equiv., morphDAST 2 equiv.	DCM, rt, 16 h	Conversion – 100 %, 15 % of **5**
SbF_3 0.05 equiv., morphDAST 2 equiv.	DCM, rt, 16 h	No reaction
PCl_3 0.05 equiv., morphDAST 2 equiv.	DCM, rt, 16 h	No reaction
PBr_3 0.05 equiv., morphDAST 2 equiv.	DCM, rt, 16 h	No reaction
$SiCl_4$ 0.05 equiv., morphDAST 2 equiv.	DCM, rt, 16 h	No reaction
$SnCl_4$ 0.05 equiv., morphDAST 2 equiv.	DCM, rt, 16 h	Conversion – 100 %
$SnCl_2$ 0.05 equiv., morphDAST 2 equiv.	DCM, rt, 16 h	Conversion – 100 %
NBS 3 equiv., NEt_3*3HF 3 equiv.	DCM, rt, 16 h	Conversion – 100 %, 60 % of **5**
$SnCl_2$ 0.05 equiv., morphDAST 2 equiv.	DCM, rt, 16 h	Conversion – 100 %
$SnCl_4$ 0.05 equiv., DAST 2 equiv.	DCM, rt, 2 h	Conversion – 100 %
$SnCl_2$ 0.05 equiv., DAST 2 equiv.	DCM, rt, 2 h	Conversion – 100 %
DAST 2 equiv.	DCM, rt, 36 h	Conversion – 100 %
CsF 3 equiv., $HgCl_2$ 0.1 equiv.	THF, rt, 16 h	Starting material. Product traces in ^{19}F
TBAF 3 equiv., $HgCl_2$ 0.1 equiv.	THF, rt, 16 h	Starting material. Product traces in ^{19}F
CsF 3 equiv., $Hg(OAc)_2$ 0.1 equiv.	THF, 60 °C, 2 h	Conversion – 80 %, **5** was formed
CsF 3 equiv., $Hg(OAc)_2$ 0.1 equiv., NEt_3*3HF 2 equiv.	THF, rt, 0.25 h	Conversion – 100 %, **5** was formed. Product traces in ^{19}F
CsF 3 equiv., $HgCl_2$ 0.1 equiv., NEt_3*3HF 2 equiv.	THF, 60 °C, 2 h	Conversion – 100 %, 70 % of **5**
AgF 3 equiv.	MeCN, rt, 3 h	Conversion – 100 %, 40 % of **5**



4, *89 %* **4a**, *85 %* **4b**, *88 %* **4c**, *91 %* **4d**, *69 %* **4e**, *72 %* **4f**, *66 %*

4g, *80 %* **4h**, *83 %* **4i**, *79 %* **4j**, *62 %* **4k**, *64 %* **4l**, *55 %*

Figure 1. The synthesis of a series of aromatic compounds **4a–l** containing the CF_2OCH_3 group

and the target samples, we calculated the Hammett constants using equations (1) and (2) [10, 14]. To ensure that the fluorine atom was not shielded by intermolecular interactions, additional ^{19}F spectra were taken at lower concentrations; the chemical shift difference remained nearly the same (**Table 2**). Based on these results, we calculated the inductive (σ_I) and resonance (σ_R) Hammett constants for the difluoro(methoxy)-methyl group as $\sigma_I = 0.2163$ and $\sigma_R = 0.0686$.

$$\Delta\delta_m^{19}F = -7.1 \times \sigma_I + 0.6 \quad (1)$$

$$\Delta\delta_p^{19}F = -7.1 \times \sigma_I - 29.5 \times \sigma_R + 0.6 \quad (2)$$

These positive values of Hammett constants indicate that the CF_2OCH_3 group acts as a moderate electron acceptor through both inductive and resonance effects. Comparing these Hammett constants with those of similar groups suggests that CF_2OCH_3 lies near CHF_2 within the series CF_3, CHF_2, CH_2F, and CH_3 (**Table 3**).

■ Conclusions

A convenient method for synthesizing aromatic compounds bearing the difluoro(methoxy) methyl group (CF_2OCH_3) *via* the fluorodesulfurization of thionoesters has been developed. By screening various fluorination conditions, an

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Table 2. ^{19}F NMR data for **4e** and **4f** at different concentrations.

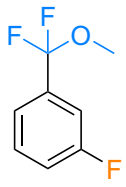
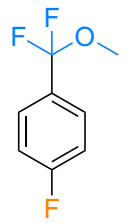
	Concentration	$\delta^{19}F(C_6H_5F)$	$\delta^{19}F(Ar)$	$\delta^{19}F(CF_2OMe)$	$\delta^{19}F(C_6H_5F) - \delta^{19}F(Ar)$ ($\Delta\delta_m^{19}F$)
 **4e**	c	-113.006	-112.07	-72.007	-0.936
	c/2	-113.008	-112.071	-72.009	-0.937
	c/4	-113.014	-112.078	-72.017	-0.936
	c/8	-113.019	-112.083	-72.023	-0.936
	c/16	-113.019	-112.083	-72.023	-0.936
	c/32	-113.022	-112.087	-72.033	-0.935
 **4f**	c	-113.005	-110.046	-71.307	-2.959
	c/2	-113.014	-110.055	-71.317	-2.959
	c/4	-113.018	-110.059	-71.321	-2.959
	c/8	-113.019	-110.059	-71.323	-2.96
	c/16	-113.019	-110.059	-71.322	-2.96
	c/32	-113.019	-110.059	-71.322	-2.96

Table 3. Hammett constants for CF_2OCH_3 and similar groups [15]

Group	σ_I	σ_R
CF_2OCH_3	0.22	0.07
CH_3	-0.08	-0.15
CH_2F	0.13	-0.02
CHF_2	0.26	0.06
CF_3	0.39	0.1
CH_2OCH_3	0.09	-0.05

$SnCl_4$/DAST combination has proven to be optimal in terms of both selectivity and yield.

The compounds **4e** and **4f** synthesized served as models to study the electronic effects of this group. The Hammett constant measurements (σ_I and σ_R) by ^{19}F NMR have shown that the difluoro(methoxy)methyl group acts as a moderate electron acceptor through both inductive and resonance pathways ($\sigma_I = 0.22$, $\sigma_R = 0.07$). The comparison with similar substituents (CF_3, CHF_2, CH_2F, CH_2OCH_3 and CH_3) suggests that CF_2OCH_3 occupies an intermediate position and is closest in overall electronic effect to CHF_2.

These findings indicate that CF_2OCH_3 can be used as an effective tool for the targeted modulation of the electronic properties of aromatic compounds. The described mild-condition synthesis of the difluoro(methoxy)methyl fragment from thionoesters broadens the scope for incorporating this group into a diverse range of molecules. Determining the electronic features of the CF_2OCH_3 group opens up promising opportunities for its further application in medicinal chemistry, materials science, and other areas of organic synthesis.

Experimental part

General information and materials

The solvents were purified according to the standard procedures. All starting materials were obtained from Enamine Ltd. NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 500 MHz for ^1H and 126 MHz for ^{13}C nucleus) and Varian Unity Plus 400 spectrometers (at 400 MHz for ^1H, 101 MHz for ^{13}C nucleus). Tetramethylsilane (^1H, ^{13}C) was used as an internal standard. GCMS analyses were performed using an Agilent 5890 Series II 5972 GCMS instrument (electron impact (EI) ionization (70 eV)). Column chromatography was performed with silica gel (200–300 mesh). The elemental analysis was carried out in the Analytical Laboratory of the Institute of Organic Chemistry, NAS of Ukraine.

The general procedure for the fluorodesulfurization (on the example of thionoester 3)

A stirred solution of methyl benzenecarbothioate (1.0 g, 6.58 mmol) in CH_2Cl_2 (30 mL) was cooled to 0°C. DAST (2.12 g, 13.16 mmol, 1.74 mL, 2.0 equiv.) was added dropwise, followed by $SnCl_4$ (85.45 mg, 328.95 μmol, 0.05 equiv.). The reaction mixture was then allowed to warm to room temperature and stirred for 2 h. It was quenched with saturated aqueous $NaHCO_3$, and the resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a crude residue. The residue was purified by silica gel column chromatography (hexanes) to give [difluoro(methoxy)methyl]benzene as a colorless liquid (0.93 g, 89% yield).

(Difluoro(methoxy)methyl)benzene (4)

A colorless liquid. Yield – 0.93 g (89%). Anal. Calcd for $C_8H_8F_2O$, %: C 60.76, H 5.10. Found, %: C 61.10, H 5.04. ^{1}H NMR (500 MHz, Chloroform-*d*), *δ*, ppm: 7.61 (2H, d, *J* = 7.4 Hz), 7.43 (3H, dt, *J* = 14.5, 6.9 Hz), 3.72 (3H, s). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*), *δ*, ppm: 133.71 (t, *J* = 32.6 Hz), 129.94, 127.75, 124.89 (t, *J* = 3.8 Hz), 122.60 (t, *J* = 257.9 Hz), 50.06 (t, *J* = 8.0 Hz). ^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*), *δ*, ppm: -72.84. GC-MS (EI), m/z: 158 $[M]^{+\cdot}$.

1-(Difluoro(methoxy)methyl)-2-methylbenzene (4a)

A colorless liquid. Yield – 0.88 g (85%). Anal. Calcd for $C_9H_{10}F_2O$, %: C 62.78, H 5.85. Found, %: C 62.80, H 5.84. ^{1}H NMR (500 MHz, Chloroform-*d*), *δ*, ppm: 7.63 (1H, d, *J* = 7.7 Hz), 7.34 (1H, t, *J* = 7.5 Hz), 7.23 (2H, d, *J* = 8.2 Hz), 3.71 (3H, s), 2.48 (3H, d, *J* = 1.9 Hz). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*), *δ*, ppm: 136.10, 131.70 (t, *J* = 30.5 Hz), 131.08, 129.84, 125.31 (t, *J* = 5.9 Hz), 124.87, 122.99 (t, *J* = 259.6 Hz), 49.92, 19.12. ^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*), δ, ppm: -73.38. GC-MS (EI), m/z: 172 $[M]^{+\cdot}$.

1-(Difluoro(methoxy)methyl)-3-methylbenzene (4b)

A colorless liquid. Yield – 0.92 g (89%). Anal. Calcd for $C_9H_{10}F_2O$, %: C 62.78, H 5.85. Found, %: C 62.47, H 5.88. ^{1}H NMR (400 MHz, Chloroform-*d*), *δ*, ppm: 7.45 (2H, d, *J* = 9.2 Hz), 7.31 (2H, dt, *J* = 13.7, 7.5 Hz), 3.74 (3H, s), 2.41 (3H, s). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*), *δ*, ppm: 138.15, 134.01 (t, *J* = 32.7 Hz), 131.22, 128.23, 125.97, 123.16 (t, *J* = 258.0 Hz), 122.45, 50.67 (t, *J* = 7.0 Hz), 21.35. ^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*), *δ*, ppm: -73.39. GC-MS (EI), m/z: 172 $[M]^{+\cdot}$.

1-(Difluoro(methoxy)methyl)-4-methylbenzene (4c)

A colorless liquid. Yield – 0.94 g (91%). Anal. Calcd for $C_9H_{10}F_2O$, %: C 62.78, H 5.85. Found, %: C 63.14, H 5.88. ^{1}H NMR (500 MHz, Chloroform-*d*), *δ*, ppm: 7.51 (2H, d, *J* = 7.9 Hz), 7.22 (2H, d, *J* = 7.9 Hz), 3.71 (3H, s), 2.39 (3H, s). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*), *δ*, ppm: 140.03, 130.85 (t, *J* = 32.7 Hz), 128.40, 124.81 (t, *J* = 3.8 Hz), 122.84 (d, *J* = 258.0 Hz), 50.10, 20.75. ^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*), *δ*, ppm: -71.32. GC-MS (EI), m/z: 172 $[M]^{+\cdot}$.

1-(Difluoro(methoxy)methyl)-2-fluorobenzene (4d)

A colorless liquid. Yield – 0.72 g (69%). Anal. Calcd for $C_8H_7F_3O$, %: C 54.55, H 4.01. Found, %: C 54.27, H 4.05. ^{1}H NMR (500 MHz, Chloroform-*d*), *δ*, ppm: 7.61 (1H, t, *J* = 7.6 Hz), 7.44 (1H, q, *J* = 7.1 Hz), 7.17 (1H, t, *J* = 7.8 Hz), 7.13 (1H, dd, *J* = 10.8, 8.4 Hz, 1H), 3.73 (3H, s). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*), *δ*, ppm: 159.37 (d, *J* = 254.3 Hz), 133.90 (d, *J* = 8.9 Hz), 131.97 (d, *J* = 8.3 Hz), 126.96 (d, *J* = 4.8 Hz), 123.10 (d, *J* = 3.8 Hz), 121.13 (t, *J* = 258.0 Hz), 116.04 (d, *J* = 21.0 Hz), 50.15. ^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*), *δ*, ppm: -72.29 (d, *J* = 14.3 Hz), -115.11 (t, *J* = 14.2 Hz). GC-MS (EI), m/z: 176 $[M]^{+\cdot}$.

1-(Difluoro(methoxy)methyl)-3-fluorobenzene (4e)

A colorless liquid. Yield – 0.75 g (72%). Anal. Calcd for $C_8H_7F_3O$, %: C 54.55, H 4.01. Found, %: C 54.16, H 4.03. ^{1}H NMR (400 MHz, Chloroform-*d*), *δ*, ppm: 7.43–7.35 (2H, m), 7.35–7.27 (1H, m), 7.14 (1H, ddd, *J* = 10.5, 5.5, 2.6 Hz), 3.71 (3H, d, *J* = 1.7 Hz). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*), *δ*, ppm: 162.41 (d, *J* = 246.8 Hz), 136.28 (td, *J* = 33.5, 7.7 Hz), 130.09 (d, *J* = 8.0 Hz), 122.22 (t, *J* = 256.8 Hz), 121.16 (q, *J* = 3.6 Hz), 117.54 (d, *J* = 21.1 Hz), 112.99 (dt, *J* = 23.9, 3.8 Hz), 50.77 (t, *J* = 7.1 Hz). ^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*), *δ*, ppm: -72.61, -112.66. GC-MS (EI), m/z: 176 $[M]^{+\cdot}$.

1-(Difluoro(methoxy)methyl)-4-fluorobenzene (4f)

A colorless liquid. Yield – 0.68 g (66%). Anal. Calcd for $C_8H_7F_3O$, %: C 54.55, H 4.01. Found, %: C 54.29, H 4.05. ^{1}H NMR (500 MHz, Chloroform-*d*), *δ*, ppm: 7.60 (2H, dd, *J* = 8.5, 5.3 Hz), 7.09 (2H, t, *J* = 8.5 Hz), 3.71 (3H, s). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*), *δ*, ppm: 163.90 (d, *J* = 249.9 Hz), 130.29 (td, *J* = 32.8, 2.8 Hz), 127.68 (dt, *J* = 8.4, 3.7 Hz), 122.67 (t, *J* = 257.7 Hz), 115.30 (d, *J* = 22.0 Hz), 50.66 (t, *J* = 7.0 Hz). ^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*), *δ*, ppm: -71.91, -110.65. GC-MS (EI), m/z: 176 $[M]^{+\cdot}$.

1-(Difluoro(methoxy)methyl)-2-methoxybenzene (4g)

A colorless liquid. Yield – 1.03 g (80%). Anal. Calcd for $C_9H_{10}F_2O_2$, %: C 57.45, H 5.36. Found, %: C 57.66, H 5.35. ^{1}H NMR (500 MHz, Chloroform-*d*), *δ*, ppm: 7.59 (1H, dd, *J* = 7.9, 1.7 Hz), 7.41 (1H, td, *J* = 7.9, 1.8 Hz), 6.97 (2H, d, *J* = 7.9 Hz), 3.88 (3H, s), 3.69 (3H, s). ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*), *δ*, ppm: 156.89, 131.49, 126.92 (t, *J* = 5.5 Hz), 122.06 (t, *J* = 258.7 Hz), 121.56 (t, *J* = 31.4 Hz), 119.40, 111.58, 55.47, 50.05. ^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*), *δ*, ppm: -73.39. GC-MS (EI), m/z: 188 $[M]^{+\cdot}$.

1-(Difluoro(methoxy)methyl)-3-methoxybenzene (4h)

A colorless liquid. Yield – 0.86 g (83%). Anal. Calcd for $C_9H_{10}F_2O_2$, %: C 57.45, H 5.36. Found, %:

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C 57.44, H 5.40. ^{1}H NMR (400 MHz, Chloroform-*d*), *δ*, ppm: 7.35 (1H, t, *J* = 8.0 Hz), 7.22 (1H, d, *J* = 7.6 Hz), 7.15 (1H, d, *J* = 2.0 Hz), 7.01 (1H, dd, *J* = 8.3, 2.6 Hz), 3.84 (3H, s), 3.73 (2H, s). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*), *δ*, ppm: 159.48, 129.48, 122.89 (t, *J* = 258.4 Hz), 121.97, 119.49, 116.47, 110.73 (d, *J* = 3.8 Hz), 55.34, 50.73 (t, *J* = 7.1 Hz). ^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*), *δ*, ppm: -73.39. GC-MS (EI), m/z: 188 $[M]^{+\cdot}$.

1-(Difluoro(methoxy)methyl)-4-methoxybenzene (4i)

A colorless liquid. Yield – 0.82 g (79%). Anal. Calcd for $C_9H_{10}F_2O_2$, %: C 57.45, H 5.36. Found, %: C 57.79, H 5.30. ^{1}H NMR (500 MHz, Chloroform-*d*), *δ*, ppm: 7.54 (2H, d, *J* = 8.5 Hz), 6.91 (2H, d, *J* = 8.7 Hz), 3.82 (3H, d, *J* = 1.1 Hz), 3.70 (3H, s). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*), *δ*, ppm: 161.12, 126.98 (t, *J* = 3.6 Hz), 126.51 (t, *J* = 33.0 Hz), 123.28 (t, *J* = 257.0 Hz), 113.55, 55.31, 50.64 (t, *J* = 7.1 Hz). ^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*), *δ*, ppm: -71.51. GC-MS (EI), m/z: 188 $[M]^{+\cdot}$.

1-(Difluoro(methoxy)methyl)-4-nitrobenzene (4j)

A yellow liquid. Yield – 0.64 g (62%). Anal. Calcd for $C_8H_7F_2NO_3$, %: C 47.30, H 3.47, N 6.90. Found, %: C 46.64, H 3.51, N 6.79. ^{1}H NMR (500 MHz, Chloroform-*d*), *δ*, ppm: 8.26 (1H, dd, *J* = 9.3, 2.6 Hz), 7.86–7.67 (1H, m), 3.75 (1H, s). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*), *δ*, ppm: 149.19, 139.92 (t, *J* = 33.7 Hz), 126.85 (t, *J* = 3.5 Hz), 123.61, 121.83 (t, *J* = 248.5 Hz), 51.01 (t, *J* = 7.1 Hz). ^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*), *δ*, ppm: -72.69. GC-MS (EI), m/z: 203 $[M]^{+\cdot}$.

1-(Difluoro(methoxy)methyl)-3-nitrobenzene (4k)

A yellow liquid. Yield – 0.66 g (64%). Anal. Calcd for $C_8H_7F_2NO_3$, %: C 47.30, H 3.47, N 6.90. Found, %: C 47.61, H 3.48, N 6.82. ^{1}H NMR (400 MHz, Chloroform-*d*), δ, ppm: 8.48 (1H, s), 8.33 (1H, dd, *J* = 8.2, 2.2 Hz), 7.95 (1H, d, *J* = 7.8 Hz), 7.63 (1H, t, *J* = 8.0 Hz), 3.78 (3H, d, *J* = 1.2 Hz). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*), *δ*, ppm: 148.06, 135.96 (t, *J* = 34.3 Hz), 131.47 (t, *J* = 3.2 Hz), 129.65, 125.37, 121.70 (t, *J* = 258.7 Hz), 121.04, 50.99 (t, *J* = 7.0 Hz). ^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*), *δ*, ppm: -72.72. GC-MS (EI), m/z: 203 $[M]^{+\cdot}$.

1-(Difluoro(methoxy)methyl)-2-nitrobenzene (4l)

A yellow liquid. Yield – 0.57 g (55%). Anal. Calcd for $C_8H_7F_2NO_3$, %: C 47.30, H 3.47, N 6.90. Found, %: C 46.61, H 3.50, N 6.80. ^{1}H NMR (400 MHz, Chloroform-*d*), *δ*, ppm: 7.86–7.72 (1H, m), 7.64 (3H, dtd, *J* = 9.2, 6.0, 2.5 Hz), 3.71 (3H, s). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*), *δ*, ppm: 148.21, 131.75, 131.56, 129.01, 127.79 (t, *J* = 4.9 Hz), 123.92, 120.84 (t, *J* = 260.1 Hz), 51.18 (t, *J* = 7.0 Hz). ^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*), *δ*, ppm: -72.75. GC-MS (EI), m/z: 203 $[M]^{+\cdot}$.

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