

UDC 542.06:547.821.2:547-302

K. I. Petko¹, A. A. Filatov^{1,2}¹ Institute of Organic Chemistry of the National Academy of Sciences of Ukraine,
5 Academician Kukhar str., 02660 Kyiv, Ukraine² Enamine Ltd., 78 Winston Churchill str., 02094 Kyiv, Ukraine

O- and N-Difluoromethylation of 2-Pyridones with Chlorodifluoromethane

Abstract

Difluoromethylation of various 2-pyridones with the available industrial reagent chlorodifluoromethane (Freon-22) has been studied. Some relationships between the ratio of difluoromethylation products and the reaction conditions, as well as the presence of substituents in the pyridine ring, have been found. The possibility of obtaining difluoromethylation products at the nitrogen atom, in some cases with a preparative yield, has been investigated.

Keywords: 2-pyridones; difluoromethylation; chlorodifluoromethane

К. І. Петко¹, А. А. Філатов^{1,2}

¹ Інститут органічної хімії Національної академії наук України,
вул. Академіка Кухаря, 5, м. Київ, 02660, Україна

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

O- та N-дифлуорометилування 2-піридонів дією хлородифлуорометану

Анотація

Досліджено дифлуорометилування різноманітних 2-піридонів дією доступного промислового реагенту хлородифлуорометану (фреон-22). Виявлено деякі залежності між співвідношенням продуктів дифлуорометилування та умовами реакції, а також наявністю замісників у піридиновому циклі. Досліджено можливість одержання продуктів дифлуорометилування за атомом нітрогену в деяких випадках з препаративним виходом.

Ключові слова: 2-піридони; дифлуорометилування; хлородифлуорометан

Citation: Petko, K. I.; Filatov, A. A. O- and N-Difluoromethylation of 2-Pyridones with Chlorodifluoromethane. *Journal of Organic and Pharmaceutical Chemistry* 2024, 22 (2), 53–58.

<https://doi.org/10.24959/ophcj.24.312997>

Received: 1 August 2024; **Revised:** 7 September 2024; **Accepted:** 11 September 2024

Copyright © 2024, K. I. Petko, A. A. Filatov. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0>).

Funding: The authors received no specific funding for this work.

Conflict of interests: The authors have no conflict of interests to declare.

■ Introduction

N-Methyl-2-pyridone is a frequently encountered motif in many pharmaceutical substances and biologically active agents [1–3]. The presence of a fluorine atom or fluorine-containing groups in a drug molecule often improves important pharmacological characteristics and reduces toxicity [4]. Therefore, N-difluoromethylpyridine-2-ones may be a potential surrogate for the bioactive molecules bearing the N-methyl-2-pyridone fragment. Moreover, previous studies have

shown that N-difluoromethyl-2-pyridone units provide the novel pharmacophore with the anti-inflammatory activity [5]. Although the first derivatives of N-difluoromethyl-2-pyridone were described as early as 1961 in the very first studies of difluoromethylation with chlorodifluoromethane [6], the yields of these compounds were low since they were usually minor products compared to the corresponding O-difluoromethyl derivatives. Importantly, unsubstituted N-difluoromethyl-2-pyridone has not been described so far.

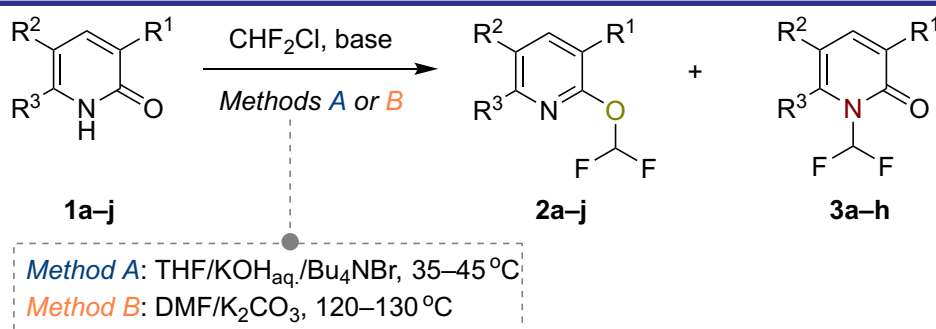
It was possible to difluoromethylate 2-pyridones at the nitrogen atom by the action of TMSCF_2Br in the presence of a hard base – potassium *tert*-butoxide. In contrast, difluoromethylation with this reagent in the presence of sodium hydrocarbonate occurs at the oxygen atom solely [7]. A few methods were developed for constructing molecules with the *N*-difluoromethyl-2-pyridone motif that did not use the direct difluoromethylation approach. *Ando et al.* developed the method for synthesizing *N*-difluoromethyl-2-pyridones starting from the corresponding 2-aminopyridines *via* their acetamide derivatives [8]. Later, *Knaus and coworkers* synthesized *N*-difluoromethylpyridine-2-ones by the interaction of $\text{FSO}_2\text{CF}_2\text{COOH}$ with the corresponding 2-halopyridines [9]. Recently, the method for obtaining *N*-difluoromethylpyridine-2-ones from pyridines unsubstituted in position 2 has also been proposed. This strategy involves difluoromethylation with bromodifluoroacetic acid esters in the presence of peroxides [10]. Although the above-mentioned methods lead to fairly high yields of the target products, they have been tested on only small loads, require expensive reagents, and are unsuitable for industrial application. Therefore, more practical protocols are still needed for the synthesis of *N*-difluoromethyl-2-pyridones. So far, the use of freon-22 remains the most convenient method of difluoromethylation applied in industry in multi-kilogram loads. In our laboratory, some studies of difluoromethylation of ambident systems of the types N=C-S [11, 12] and N=C-C [13] by chlorodifluoromethane (Freon-22) were performed. The results show that, depending on the temperature and alkali excess, one can alter the regioselectivity of the reaction. Under more harsh conditions, the products of difluoromethylation at the nitrogen atom

can be a major one. In this work, we studied the dependence of the *O*- and *N*-isomers ratio on the difluoromethylation conditions during the interaction of chlorodifluoromethane with 2-pyridone derivatives.

Results and discussion

The parent pyridine-2-one (**1a**) and its derivatives containing halogen atoms or/and methyl groups (**1b–j**) were chosen as starting compounds (**Scheme**). Two main methods of difluoromethylation were studied on a series of 2-pyridones.

The “soft” *Method A* employed the “THF/35% aqueous KOH” system in the presence of a phase-transfer catalyst at a relatively low temperature (35–45 °C) – the kinetic reaction control. The “hard” *Method B* was used in the “DMF/potassium carbonate” system at 120–130 °C – the thermodynamic reaction control. Both methods, *A* and *B*, were not accompanied by side processes and led to high total yields of the target products. The lower yields of compounds **2a** and **3a** when using *Method B* were explained by difficulties in separating these products from the solvent (DMF). Products **2a–h** and **3a–h**, in all cases, had a sufficiently high difference in volatility and the difference in boiling points was *ca.* 30–40 °C. Isomers **2** and **3** could be separated in all cases by fractional distillation using an effective refluxing column. As expected, by analogy with our earlier works [11–13] when using more harsh conditions the ratio of *N*-difluoromethylation products (**3a–h**) increased in almost all cases compared to the mild conditions, but did not always lead to preparative yields of products **3a–h**. The decisive factor directing the reaction toward *O*- CHF_2 products **2** or *N*- CHF_2 counterparts **3** was the presence of substituents. While unsubstituted 2-pyridone (**1a**)



a: $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$; **b:** $\text{R}^1 = \text{Br}$, $\text{R}^2 = \text{R}^3 = \text{H}$; **c:** $\text{R}^1 = \text{F}$, $\text{R}^2 = \text{Br}$, $\text{R}^3 = \text{H}$; **d:** $\text{R}^1 = \text{Cl}$, $\text{R}^2 = \text{Br}$, $\text{R}^3 = \text{H}$; **e:** $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Br}$, $\text{R}^3 = \text{H}$; **f:** $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Br}$, $\text{R}^3 = \text{Me}$; **g:** $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Br}$, $\text{R}^3 = \text{H}$; **h:** $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{I}$, $\text{R}^3 = \text{H}$; **i:** $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{F}$; **j:** $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{Cl}$

Scheme. Difluoromethylation of 2-pyridone derivatives

was difluoromethylated mainly at the oxygen atom (regardless of the conditions the yield of **3a** did not exceed 20%), the presence of halogen atoms in position 3 reducing nucleophilicity and creating some steric hindrances (compounds **1b–d**) resulted in drastic increase in the yield of products **3b–d**. Thus, the yields of **3b–d** became comparable with those for the *O*-CHF₂ products **2b–d** when the reaction was carried out under mild conditions (*Method A*), and compounds **3b–d** appeared to be major products under more harsh conditions (*Method B*). On the contrary, the presence of the methyl group in position 3 (**1e**) completely inhibited the formation of product **3e** under mild conditions and resulted in a low yield of **3e** in *Method B*. Apparently, the methyl group acting as a donor increased the nucleophilicity of the oxygen atom. Similarly, when difluoromethylating compound **1f** (containing the methyl group in position 6) under mild conditions only compound **2f** was formed. However, with the use of *Method B*, the yield of compound **3f** was higher compared to compound **3e** similarly obtained. Again, the viable explanation is the donor effect of the methyl group increasing the nucleophilicity of the nitrogen atom and leading to a slight increase in the yield of compound **3f**, even despite the steric hindrances created by the α -CH₃ substituent. The presence of the halogen atom, in position 5, especially in the case of compound **1h** containing the iodine atom also led to an increase in the yield of *N*-difluoromethylation products. Thus, even under the mild conditions of *Method A*, the yield of compound **3h** exceeded 30%, and in the case of *Method B*, difluoromethylation products **2h** and **3h** were formed in approximately equal proportions. The presence of the halogen atom in position 6, on the contrary,

completely excluded the formation of *N*-difluoromethylation products. The electron-withdrawing effect of the halogen reduced the nucleophilicity of the nitrogen atom, so we were unable to obtain compounds **3i** and **3j** under either mild or harsh conditions. Only the corresponding *O*-derivatives **2i** and **2j** were obtained with good yields. The results of the studies are summarized in **Table**.

■ Conclusion

Difluoromethylation of various 2-pyridones has been studied using the available industrial reagent – Freon-22. It has been shown that pyridin-2-ones under more severe conditions are difluoromethylated largely at the nitrogen atom. The presence of halogen atoms in positions 3 and 5 of the pyridine ring increases the contribution of difluoromethylation products at the nitrogen atom, whereas the presence of halogen atoms in position 6 completely excludes difluoromethylation at the nitrogen atom.

■ Experimental part

Melting points were measured in open capillaries and were given uncorrected. ¹H NMR (400 MHz, CDCl₃) and ¹⁹F NMR (376 MHz, CDCl₃) spectra were recorded on a Varian-Mercury-400 spectrometer using TMS and CCl₃F as internal standards. The reaction progress was controlled by TLC on Silufol 254 plates.

The general procedure of difluoromethylation of 2-pyridones (Method A)

The solution of the starting 2-pyridones **1a–j** (0.3 mol) in THF (400 mL) and Bu₄NBr (1 g) were stirred and treated with the solution of KOH

Table. The results of the experiments

Starting compound	R ¹	R ²	R ³	Method A		Method B	
				Isolated yield (2+3)	Ratio 2:3	Isolated yield (2+3)	Ratio 2:3
1a	H	H	H	72	10:1	42 ^a	4:1
1b	Br	H	H	78	1:1	74	1:2
1c	F	Br	H	69	2:1	64	5:4
1d	Cl	Br	H	82	5:4	71	2:3
1e	CH ₃	Br	H	89	100:0	76	4:1
1f	H	Br	CH ₃	75	100:0	72	3:1
1g	H	Br	H	85	3:1	73	3:2
1h	H	I	H	78	8:5	74	1:1
1i	H	H	F	78	100:0	67 ^a	100:0
1j	H	H	Cl	80	100:0	72	100:0

Note: ^a Products **2a** and **2i** synthesized by *Method B* contain a residual DMF. The ratio 2:3 in the case of **2a** and **3a** was measured according to ¹⁹F NMR spectra of the reaction mixture

(90 g, 1.6 mol) in H₂O (160 mL). Chlorodifluoromethane (Freon-22) was bubbled through the vigorously stirred reaction mixture at 30–45 °C until the absorption of the gas ceased (the exothermic effect was observed). If some amount of the starting 2-pyridone remained unreacted (according to the TLC control), the additional KOH (30 g) was added, and Freon-22 was bubbled until the absorption of the gas ceased. The overall time of the reaction was about 4–5 hours. Then, water (100 mL) was added, the product was extracted with hexane (2×300 mL), the organic layer was separated, dried over anhydrous K₂CO₃, and the solvent was evaporated under reduced pressure. The mixture of isomers was separated by fractional distillation, followed by crystallization in the cases of solid products **3**.

The general procedure of difluoromethylation of 2-pyridones (Method B)

To a vigorously stirred solution of the starting 2-pyridone **1a–j** (0.3 mol) in DMF (150 mL), anhydrous powdered K₂CO₃ (86 g, 0.6 mol) was added, and the reaction mixture was heated to 110 °C. Chlorodifluoromethane (Freon-22) was bubbled through the vigorously stirred reaction mixture (the exothermic effect was observed), and the temperature reached 130 °C without external heating. The bubbling was continued until the absorption of the gas ceased, and the temperature dropped to 30–45 °C. Water (500 mL) was added, and the product was extracted with hexane (2×300 mL). Then, the organic layer was separated, the residual DMF was washed off with water (2×300 mL), and the organic extracts were dried over anhydrous K₂CO₃. After that, the solvent was evaporated under reduced pressure. The mixture of isomers was separated by fractional distillation, followed by crystallization in the cases of solid products **3**.

2-Difluoromethoxypyridine (**2a**)

A colorless liquid. Yield – 26.15 g, 62% (Method A); 12.91 g, 30% (Method B). B. p. 50–52 °C (30 Torr). Anal. Calcd for C₆H₅F₂NO, %: C 49.66, H 3.47, N 9.65. Found, %: C 49.75, H 3.48, N 9.57. ¹H NMR (400 MHz, CDCl₃), δ, ppm: 6.87 (1H, d, *J* = 5 Hz), 7.05–7.10 (1H, m, ArH), 7.47 (1H, t, *J* = 72 Hz, O-CHF₂), 7.70–7.75 (1H, m, ArH). ¹⁹F NMR (376 MHz, CDCl₃), δ, ppm: -89.1 (d, *J* = 72 Hz, O-CHF₂).

2-Difluoromethoxy-3-bromopyridine (**2b**)

A colorless liquid. Yield – 26.21 g, 39% (Method A); 16.80 g, 25% (Method B). B. p. 44–46 °C (1 Torr). The spectral data is consistent with the ones previously published [14].

2-Difluoromethoxy-3-fluoro-5-bromopyridine (**2c**)

A colorless liquid. Yield – 33.40 g, 46% (Method A); 25.41 g, 35% (Method B). B. p. 52–54 °C (1 Torr). Anal. Calcd for C₆H₃BrF₃NO, %: C 29.78, H 1.25, N 5.79. Found, %: C 29.69, H 1.28, N 5.88. ¹H NMR (400 MHz, CDCl₃), δ, ppm: 7.48 (1H, t, *J* = 72 Hz, O-CHF₂), 7.68 (1H, dd, ³*J*_{HF} = 8 Hz, ⁴*J*_{HH} = 2 Hz), 8.09 (1H, d, *J* = 2 Hz). ¹⁹F NMR (376 MHz, CDCl₃), δ, ppm: -88.7 (d, *J* = 72 Hz, O-CHF₂).

2-Difluoromethoxy-3-chloro-5-bromopyridine (**2d**)

A colorless liquid. Yield – 34.90 g, 45% (Method A); 32.60 g, 42% (Method B). B. p. 55–57 °C (1 Torr). Anal. Calcd for C₆H₃BrClF₂NO, %: C 27.88, H 1.17, N 5.42. Found, %: C 27.75, H 1.28, N 5.47. ¹H NMR (400 MHz, CDCl₃), δ, ppm: 7.47 (1H, t, *J* = 72 Hz, O-CHF₂), 7.91 (1H, d, *J* = 2 Hz), 8.15 (1H, d, *J* = 2 Hz). ¹⁹F NMR (376 MHz, CDCl₃), δ, ppm: -88.2 (d, *J* = 72 Hz, O-CHF₂).

2-Difluoromethoxy-3-methyl-5-bromopyridine (**2e**)

A colorless liquid. Yield – 63.54 g, 89% (Method A); 42.84 g, 60% (Method B). B. p. 50–52 °C (1 Torr). Anal. Calcd for C₇H₆BrF₂NO, %: C 35.32, H 2.54, N 5.88. Found, %: C 35.45, H 2.42, N 5.97. ¹H NMR (400 MHz, CDCl₃), δ, ppm: 2.27 (s, 1H, CH₃), 7.43 (1H, t, *J* = 72 Hz, O-CHF₂), 7.57 (1H, d, *J* = 2 Hz), 8.02 (1H, d, *J* = 2 Hz). ¹⁹F NMR (376 MHz, CDCl₃), δ, ppm: -89.5 (d, *J* = 72 Hz, O-CHF₂).

2-Difluoromethoxy-5-bromo-6-methylpyridine (**2f**)

A colorless liquid crystallized in a refrigerator. Yield – 53.40 g, 75% (Method A); 35.71 g, 50% (Method B). B. p. 50–52 °C (1 Torr). M. p. 17–19 °C. Anal. Calcd for C₇H₆BrF₂NO, %: C 35.32, H 2.54, N 5.88. Found, %: C 35.42, H 2.55, N 6.07. ¹H NMR (400 MHz, CDCl₃), δ, ppm: 2.58 (s, 1H, CH₃), 6.64 (1H, d, *J* = 6 Hz), 7.45 (1H, t, *J* = 72 Hz, O-CHF₂), 7.78 (1H, d, *J* = 6 Hz). ¹⁹F NMR (376 MHz, CDCl₃), δ, ppm: -90.2 (d, *J* = 72 Hz, O-CHF₂).

2-Difluoromethoxy-5-bromopyridine (**2g**)

A colorless liquid. Yield – 42.33 g, 63% (Method A); 30.241 g, 35% (Method B). B. p. 45–47 °C (1 Torr). The spectral data is consistent with the ones previously published [8].

2-Difluoromethoxy-5-iodopyridine (**2h**)

A colorless liquid. Yield – 39.02 g, 48% (Method A); 30.08 g, 37% (Method B). B. p. 64–66 °C (1 Torr). Anal. Calcd for C₆H₄IF₂NO, %: C 26.59, H 1.49, N 5.17. Found, %: C 26.64, H 1.68, N 5.32. ¹H NMR (400 MHz, CDCl₃), δ, ppm: 6.72 (1H, d, *J* = 6 Hz), 7.41 (1H, dd, ³*J*_{HH} = 6 Hz, ⁴*J*_{HH} = 2 Hz),

7.36 (1H, t, $J = 72$ Hz, O-CHF₂), 7.98 (1H, d, $J = 6$ Hz), 8.42 (1H, s). ¹⁹F NMR (376 MHz, CDCl₃), δ , ppm: -88.2 (d, $J = 72$ Hz, O-CHF₂).

2-Difluoromethoxy-6-fluoropyridine (2i)

A colorless liquid. Yield – 39.12 g, 80% (Method A); 31.18 g, 65% (Method B). B. p. 75–77 °C (30 Torr). The spectral data is consistent with the published previously [14].

2-Difluoromethoxy-6-chloropyridine (2j)

A colorless liquid. Yield – 43.02 g, 80% (Method A); 37.78 g, 70% (Method B). B. p. 29–30 °C (1 Torr). The spectral data is consistent with the ones previously published [14].

1-Difluoromethylpyridine-2(1H)-one (3a)

A colorless liquid crystallized in a refrigerator. Yield – 3.45 g, 8% (Method A); 7.21 g, 15% (Method B). B. p. 92–94 °C (30 Torr). M. p. 7–9 °C. Anal. Calcd for C₆H₅F₂NO, %: C 49.66, H 3.47, N 9.65. Found, %: C 49.54, H 3.42, N 9.78. ¹H NMR (400 MHz, CDCl₃), δ , ppm: 6.24 (1H, t, $J = 5$ Hz), 6.48 (1H, d, $J = 5$ Hz), 7.27–7.35 (2H, m, ArH), 7.63 (1H, t, $J = 60$ Hz, N-CHF₂). ¹⁹F NMR (376 MHz, CDCl₃), δ , ppm: -103.9 (d, $J = 60$ Hz, N-CHF₂).

1-Difluoromethyl-3-bromo-pyridine-2(1H)-one (3b)

A white solid. Yield – 26.12 g, 39% (Method A); 33.40 g, 50% (Method B). B. p. 73–75 °C (1 Torr), M. p. 69–70 °C (hexane), lit. [10] – oil. The spectral data is consistent with the ones previously published [10].

1-Difluoromethyl-3-fluoro-5-bromopyridine-2(1H)-one (3c)

A white low-melting point solid. Yield – 16.70 g, 23% (Method A); 21.78 g, 30% (Method B). B. p. 85–88 °C (1 Torr). M. p. 34–35 °C (hexane). Anal. Calcd for C₆H₃BrF₃NO, %: C 29.78, H 1.25, N 5.79. Found, %: C 29.72, H 1.19, N 5.69. ¹H NMR (400 MHz, CDCl₃), δ , ppm: 7.21 (1H, dd, ³J_{HF} = 8 Hz, ⁴J_{HH} = 2 Hz), 7.44 (1H, d, $J = 2$ Hz), 7.66 (1H, t, $J = 60$ Hz, N-CHF₂). ¹⁹F NMR (376 MHz, CDCl₃), δ , ppm: -103.8 (d, $J = 60$ Hz, N-CHF₂).

1-Difluoromethyl-3-chloro-5-bromopyridine-2(1H)-one (3d)

A white low-melting point solid. Yield – 27.97 g, 36% (Method A); 38.85 g, 50% (Method B). B. p. 90–92 °C (1 Torr). M. p. 41–42 °C (hexane). Anal.

Calcd for C₆H₃BrClF₂NO, %: C 27.88, H 1.17, N 5.42. Found, %: C 27.80, H 1.22, N 5.31. ¹H NMR (400 MHz, CDCl₃), δ , ppm: 7.54 (1H, d, $J = 2$ Hz), 7.62 (1H, d, $J = 2$ Hz), 7.65 (1H, t, $J = 60$ Hz, N-CHF₂). ¹⁹F NMR (376 MHz, CDCl₃), δ , ppm: -102.9 (d, $J = 60$ Hz, N-CHF₂).

1-Difluoromethyl-3-methyl-5-bromopyridine-2(1H)-one (3e)

A white low-melting point solid. Yield – 10.71 g, 15% (Method B). B. p. 83–85 °C (1 Torr). M. p. 37–38 °C (hexane). Anal. Calcd for C₇H₆BrF₂NO, %: C 35.32, H 2.54, N 5.88. Found, %: C 35.51, H 2.52, N 6.17. ¹H NMR (400 MHz, CDCl₃), δ , ppm: 2.15 (s, 1H, CH₃), 7.29 (1H, d, $J = 2$ Hz), 7.46 (1H, d, $J = 2$ Hz), 7.65 (1H, t, $J = 60$ Hz, N-CHF₂). ¹⁹F NMR (376 MHz, CDCl₃), δ , ppm: -103.9 (d, $J = 60$ Hz, N-CHF₂).

1-Difluoromethyl-5-bromo-6-methylpyridine-2(1H)-one (3f)

A white low-melting point solid. Yield – 12.85 g, 18% (Method B). B. p. 83–85 °C (1 Torr). M. p. 40–41 °C (hexane). Anal. Calcd for C₇H₆BrF₂NO, %: C 35.32, H 2.54, N 5.88. Found, %: C 35.44, H 2.61, N 6.02. ¹H NMR (400 MHz, CDCl₃), δ , ppm: 2.23 (s, 1H, CH₃), 7.31 (1H, d, $J = 6$ Hz), 7.42 (1H, d, $J = 2$ Hz), 7.81 (1H, t, $J = 60$ Hz, N-CHF₂). ¹⁹F NMR (376 MHz, CDCl₃), δ , ppm: -103.2 (d, $J = 60$ Hz, N-CHF₂).

1-Difluoromethyl-5-bromopyridine-2(1H)-one (3g)

A white solid. Yield – 14.11 g, 21% (Method A); 20.16 g, 30% (Method B). B. p. 73–75 °C (1 Torr). M. p. 77–78 °C (hexane), lit. [8] – 75–76 °C. The spectral data is consistent with the ones previously published [8].

1-Difluoromethyl-5-iodopyridine-2(1H)-one (3h)

A white solid. Yield – 24.79 g, 30% (Method A); 30.11 g, 37% (Method B). B. p. 95–97 °C (1 Torr). M. p. 71–72 °C (hexane). Anal. Calcd for C₆H₄IF₂NO, %: C 26.59, H 1.49, N 5.17. Found, %: C 26.66, H 1.55, N 5.27. ¹H NMR (400 MHz, CDCl₃), δ , ppm: 6.33 (1H, d, $J = 7$ Hz), 7.41 (1H, dd, ³J_{HH} = 7 Hz, ⁴J_{HH} = 2 Hz), 7.57 (1H, t, $J = 60$ Hz, N-CHF₂), 7.63 (1H, d, $J = 2$ Hz). ¹⁹F NMR (376 MHz, CDCl₃), δ , ppm: -101.8 (d, $J = 60$ Hz, N-CHF₂).

References

- Lindenblad, G. E.; Kaihara, M.; Price, J. M. The occurrence of N-Methyl-2-pyridone-5-carboxylic acid and its glycine conjugate in normal human urine. *J. Biol. Chem.* **1956**, *219*, 893–901. [https://doi.org/10.1016/S0021-9258\(18\)65747-3](https://doi.org/10.1016/S0021-9258(18)65747-3).
- Gray, D.; Gallagher, T. A Flexible Strategy for the Synthesis of Tri- and Tetracyclic Lupin Alkaloids: Synthesis of (+)-Cytisine, (±)-Anagryrine, and (±)-Thermopsine. *Angew. Chem. Int. Ed.* **2006**, *45* (15), 2419–2423. <https://doi.org/10.1002/anie.200504015>.
- Khalil, I. M.; Barker, D.; Copp, B. R. Bioinspired synthesis of the pyridoacridine marine alkaloids: demethyldeoxyamphimedine, deoxyamphimedine, and amphimedine. *J. Org. Chem.* **2016**, *81* (1), 282–289. <https://doi.org/10.1021/acs.joc.5b02312>.

- Kirk, K. L. Fluorination in Medicinal Chemistry: Methods, Strategies, and Recent Developments. *Org. Process Res. Dev.* **2008**, *12* (2), 305–321. <https://doi.org/10.1021/op700134j>.
- Chowdhury, M. A.; Abdellatif, K. R. A.; Dong, Y.; Das, D.; Suresh, M. R.; Knaus, E. E. Synthesis of Celecoxib Analogues Possessing a *N*-Difluoromethyl-1,2-dihydropyrid-2-one 5-Lipoxygenase Pharmacophore: Biological Evaluation as Dual Inhibitors of Cyclooxygenases and 5-Lipoxygenase with Anti-Inflammatory Activity. *J. Med. Chem.* **2009**, *52* (6), 1525–1529. <https://doi.org/10.1021/jm8015188>.
- Shen, T. Y.; Lucas, S.; Sarett, L. H. Chlorodifluoromethane as a difluoromethylating agent. *Tetr. Lett.* **1961**, *2* (2), 43–47. [https://doi.org/10.1016/S0040-4039\(01\)99204-4](https://doi.org/10.1016/S0040-4039(01)99204-4).
- Zhu, Z.; Krishnamurti, V.; Ispizua-Rodriguez, X.; Barrett, C.; Prakash S. Chemoselective *N*- and *O*-difluoromethylation of 2-Pyridones, Isoquinolinones, and Quinolinones with TMSCF₂Br. *Org. Lett.* **2021**, *23* (16), 6494–6498. <https://doi.org/10.1021/acs.orglett.1c02305>.
- Ando, M.; Wada, T.; Sato, N. Facile one-pot synthesis of *N*-difluoromethyl-2-pyridone derivatives. *Org. Lett.* **2006**, *8* (17), 3805–3808. <https://doi.org/10.1021/ol061481f>.
- Yu, G.; Praveen Rao, P. N.; Chowdhury, M. A.; Abdellatif, K. R. A.; Dong, Y.; Das, D.; Velazquez, C. A.; Suresh, M. R.; Knaus, E. E. Synthesis and biological evaluation of *N*-difluoromethyl-1,2-dihydropyrid-2-one acetic acid regioisomers: dual inhibitors of cyclooxygenases and 5-lipoxygenase. *Bioorg. Med. Chem. Lett.* **2010**, *20* (7), 2168–2173. <https://doi.org/10.1016/j.bmcl.2010.02.040>.
- Zhou, S.; Hou, X.; Yang, K.; Guo, M.; Zhao, W.; Tang, X.; Wang, G. Direct synthesis of *N*-difluoromethyl-2-pyridones from pyridines. *J. Org. Chem.* **2021**, *86* (9), 6879–6887. <https://doi.org/10.1021/acs.joc.1c00228>.
- Petko, K. I.; Yagupolskii, L. M. Unusual difluoromethylation of 2-mercaptoazoles. *J. Fluor. Chem.* **2001**, *108* (2), 211–214. [https://doi.org/10.1016/S0022-1139\(01\)00350-5](https://doi.org/10.1016/S0022-1139(01)00350-5).
- Petko, K. I.; Yagupolskii, L. M. Difluoromethylation of 5-sulfanyl-tetrazoles. *Russ. J. Org. Chem.* **2004**, *40* (4), 601–602. <https://doi.org/10.1023/B:RUJO.0000036093.66034.cc>.
- Petko, K. I.; Sokolenko, T. M.; Yagupolskii, L. M. Difluoromethylation of Heterocyclic Compounds Containing an N=C-C Ambident Nucleophilic System. *Russ. J. Org. Chem.* **2005**, *41* (3), 429–433. <https://doi.org/10.1007/s11178-005-0182-2>.
- Landelle, G.; Schmitt, E.; Pannosian, A.; Vors, J.-P.; Pazenok, S.; Jeschke, P.; Gutbrod, O.; Leroux, F. R. Tri- and difluoromethylated *N*-based heterocycles – synthesis and insecticidal activity of novel F₃CO- and F₂HCO- analogs of Imidacloprid and Thiacloprid. *J. Fluor. Chem.* **2017**, *203*, 155–165. <https://doi.org/10.1016/j.jfluchem.2017.08.006>.

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>.