Facile synthesis of 6-organyl-4-(trifluoromethyl)pyridin-2(1*H*)-ones and their polyfluoroalkyl-containing analogs*

S. O. Kushch,[a] M. V. Goryaeva,[a] Ya. V. Burgart,[a] G. A. Triandafilova,[b] K. O. Malysheva,[b] O. P. Krasnykh,[b] N. A. Gerasimova,[c] N. P. Evstigneeva,[c] and V. I. Saloutin[a]★

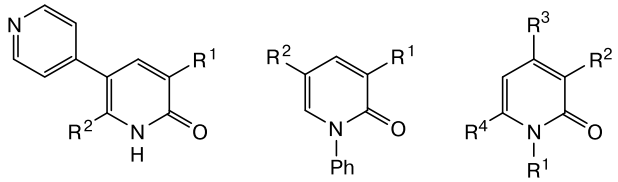
[a]*I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 22/20 ul. S. Kovalevskoi, 620108 Yekaterinburg, Russian Federation. Fax:+7 (343) 374 5954. E-mail: saloutin@ios.uran.ru*
[b]*Perm National Research Polytechnic University, 29 Komsomolskii prosp., 614990 Perm, Russian Federation*
[c]*Ural Research Institute of Dermatovenereology and Immunopathology, 8 ul. Shcherbakova, 620076 Yekaterinburg, Russian Federation*

The three-component cyclization of 3-polyfluoroalkyl-3-oxopropanoates and methyl ketones with ammonium acetate affords 6-organyl-4-(polyfluoroalkyl)pyridin-2(1*H*)-ones (organyl is alkyl, aryl, or hetaryl). The synthesized pyridones were evaluated for antifungal, antibacterial, and analgesic activity.

Key words: ethyl trifluoroacetoacetate, 3-polyfluoroalkyl-3-oxopropanoates, methyl ketones, ammonium acetate, three-component reaction, 4-(trifluoromethyl)pyridin-2-ones.

The pyridin-2-one scaffold is an important structural motif in organic chemistry. Compounds of this series are not only used as the starting reagents for the generation of new organic molecules[1—3] but also have found a recent application as ligands in various palladium-catalyzed reactions.[4—6] These heterocyclic molecules also have attracted attention due to their biological properties. The pyridin-2-one scaffold is present in many biologically active natural products,[2,3,7,8] such as the antibiotic ilicocolin H,[9] the cytostatic agent pyridoxatin,[10] the mycotoxin sambutoxin,[11] thrombostatics calipyridones,[12] and numerous polycyclic alkaloid derivatives,[2,13] in particular (±)-cytisine, irinotecan, (+)-hosieine, leporin A, huperzine A,[14] camptothecin,[15] and fredericamycin A.[16] The following synthetic drugs were designed based on the pyridin-2-one scaffold:[17—22] amrinone[17] (**D1**), milrinone[18] (**D2**), pirfenidone[19] (**D3**), perampanel[20] (**D4**), ricinine[21] (**D5**), and ciclopirox[22] (**D6**). Besides, pyridin-2-ones were used to produce biosensors.[23]

Natural and synthetic pyridin-2-one derivatives proved to be anticancer, antibacterial, antifungal, antiviral, anti-inflammatory, and psychotherapeutic agents.[3,24—26] Recently, pyridin-2-one natural products were found to act as efficient SARS-CoV-2 main protease inhibitors.[27]



D1, **D2** **D3**, **D4** **D5**, **D6**

Compound	R^1	R^2	R^3	R^4
D1	NH_2	H	—	—
D2	CN	Me	—	—
D3	H	Me	—	—
D4	2-NCC_6H_4	Pyridin-2-yl	—	—
D5	Me	CN	OMe	H
D6	OH	H	Me	*cyclo*-C_6H_{11}

Of particular promise in the synthesis of biologically active compounds are CF_3-substituted heterocycles[28] because the presence of a trifluoromethyl group in organic molecules has a significant effect on their physical and chemical properties, metabolic stability, solubility, and lipophilicity.[29] Some 4-(trifluoromethyl)-pyridin-2-ones exhibit antiretroviral activity, and their representative, doravirine (**D7**), was approved as the initial therapy in patients with HIV/AID.[30] 3-Cyano-4-(trifluoromethyl)pyridin-2-ones can inhibit α-synuclein

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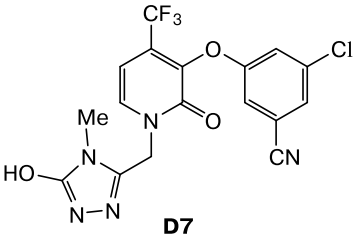
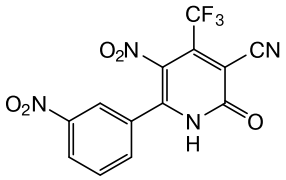
aggregation and prevent degeneration of dopaminergic neurons. One compound of this family, SynuClean-D (**D8**), is considered as a promising drug candidate for the treatment of Parkinson's disease.[31] Trifluoromethyl-containing pyridin-2-ones proved to be efficient ligands in Pd-catalyzed CH-functionalization reactions.[32]



D7

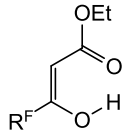


D8

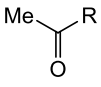
Numerous approaches were developed for the formation of 4-(trifluoromethyl)pyridin-2-ones[33—41] and their non-fluorinated analogs.[42—46] However, despite the relative variability of the synthetic approaches, all these methods suffer from drawbacks, such as the involvement of many steps, the use of difficultly accessible reagents, and the application of special cryogenic equipment. Therefore, the development of a facile synthesis of such attractive compounds as 4-(trifluoromethyl)pyridin-2-ones is a challenging problem.

Recently, we proposed to use the three-component cyclization of 3-polyfluoroalkyl-3-oxopropanoates with methyl ketones and diamines or amino alcohols as a versatile route to diverse hydrogenated bi-, tri-, and tetracyclic pyridin-2-one derivatives, some of which exhibit antiviral, anticancer, antifungal, and analgesic activity.[47—51] A series of *N*-functionalized 4-(polyfluoroalkyl)pyridin-2-ones with tuberculostatic activity were synthesized by the acid cleavage of 7-hydroxy-7-polyfluoroalkylhexahydroimidazo[1,2-*a*]pyridin-5-ones.[52]

Here, we made an attempt to apply this one-pot method to synthesize hydroxydihydropyridinones **3** and 4-(polyfluoroalkyl)pyridin-2(1*H*)-ones **4** by using ammonia in the cyclization with 3-polyfluoroalkyl-3-oxopropanoates **1** and methyl ketones **2**. The utilization of ammonia was expected to provide the formation of the pyridine ring unlike the similar transformations of alkylamines studied previously, which resulted in the alternative formation of aminocyclohexenones.[53] The employment of various fluorine-containing keto esters **1a—d** and alkyl, aryl, and hetaryl methyl ketones **2a—k** makes it possible to vary the fluorinated and non-fluorinated substituents at the C(4) and C(6) positions in the resulting pyridones.



1a—d

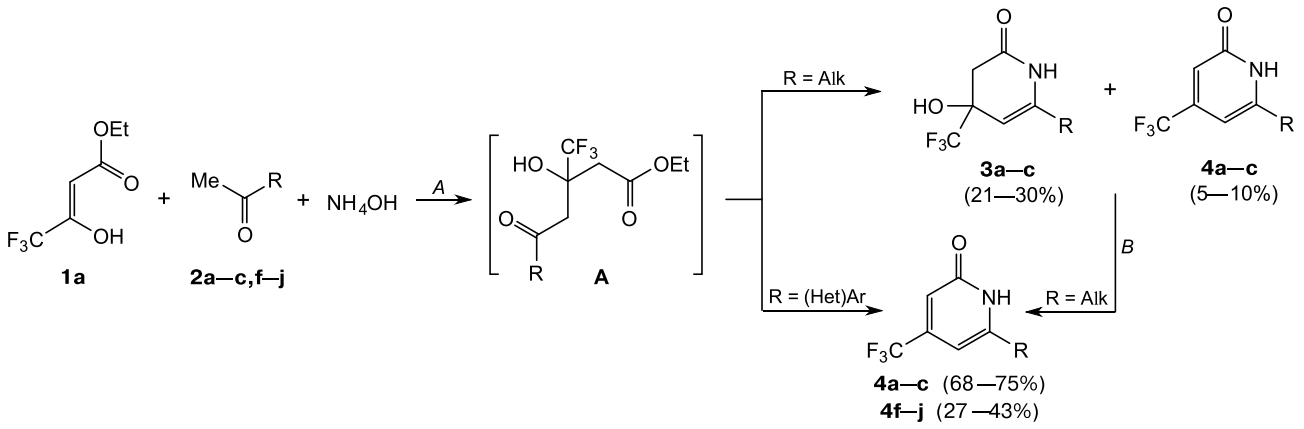


2a—k

1: R^F = CF_3 (**a**), $H(CF_2)_2$ (**b**), C_2F_5 (**c**), C_3F_7 (**d**)
2: R = Me (**a**), Et (**b**), Bu (**c**), Pr^i (**d**), Bu^t (**e**), Ph (**f**), 4-MeC_6H_4 (**g**), 2,4-$Me_2C_6H_3$ (**h**), furan-2-yl (**i**), thiophen-2-yl (**j**), pyridin-2-yl (**k**)

First, we studied the reaction of trifluoroacetoacetate **1a** and methyl ketones **2a—c,f—j** with 30% aqueous ammonia (Scheme 1, method *A*). We used 1,4-dioxane as the solvent, which was previously utilized for the

Scheme 1



R= Me (**a**), Et (**b**), Bu (**c**), Ph (**f**), 4-MeC_6H_4 (**g**), 2,4-MeC_6H_3 (**h**), furan-2-yl (**i**), thiophen-2-yl (**j**)

Reagents and conditions: method *A*: 1,4-dioxane, 60 °C; method *B*: toluene, TsOH, Δ.

synthesis of fused pyridones by three-component cyclizations.[47—51] The progress of the reactions was monitored by GLC and ^{19}F NMR spectroscopy. At room temperature, the reactions with aqueous ammonia proved to be inefficient. Therefore, we performed the synthesis at 60 °C. The heating for 10—12 h resulted in the formation of aldol **A** as the major product (~65—78%). Previously, we obtained this aldol in the reaction of keto ester **1a** with acetone **2a**.[53] Meanwhile, crystals were obtained within 3—7 days by concentrating the reaction mixture. According to GLC and NMR analysis, these crystals were either hydroxydihydropyridin-5-ones **3** or pyridin-5-ones **4**.

The reactions of ester **1a** with alkyl methyl ketones **2a—c** and aqueous ammonia gave hydroxydihydropyridinones **3a—c** as the major products with a small impurity of dehydrated analogs **4a—c** (~5—10%). The latter compounds apparently formed during the isolation. To confirm this assumption, we heated compounds **3a—c** in 1,4-dioxane and found that, under these conditions, the dehydration was slow. The efficiency of the dehydration was higher when the reaction was performed under reflux in toluene in the presence of *p*-toluenesulfonic acid. In this case, we obtained 2-pyridones **4a—c** (see Scheme 1, method *B*).

As opposed to the transformations using alkyl methyl ketones **2a—c**, the reactions with aryl methyl ketones **2f—j** accomplished under similar conditions (see Scheme 1, method *A*) immediately afforded dehydrated pyridin-2-ones **4f—j**. Apparently, the hydroxy derivatives containing the conjugated (het)aryl substituent have a lower dehydration barrier, resulting in the ease of their formation.

Evidently, the presence of water adversely affects the reaction. Therefore, were decided to perform the three-component reaction of keto ester **1a** and acetone **2a** with ammonium acetate in the presence of trimethylamine, which is required for the transformation of the salt into the base (Scheme 2).

Using this reaction, we conducted the optimization of the reaction conditions (Table 1, runs *1—9*). The following optimal conditions were found for the formation of product **4a**: the heating in 1,4-dioxane at 60 °C (run *8*). Under these conditions, product **4a** was ob-

Scheme 2

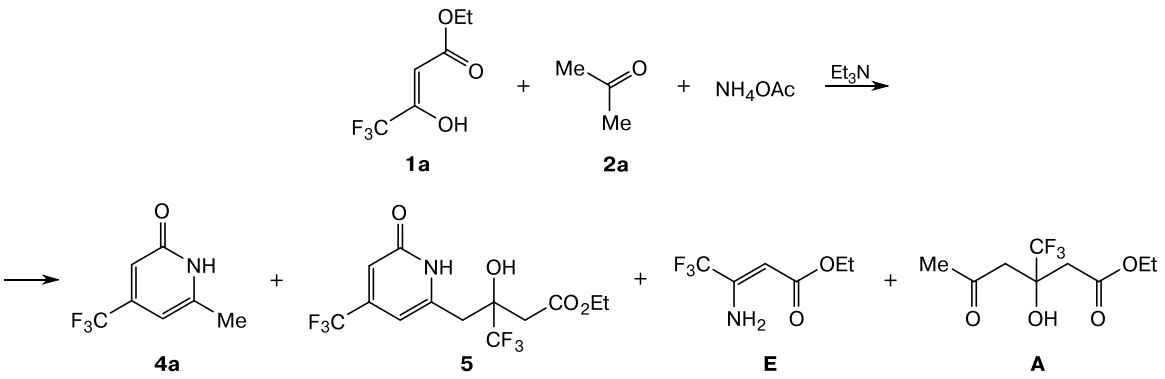


Table 1. Optimization of the reaction conditions for ester **1a**, acetone (**2a**), and ammonium acetate[a]

Run	Solvent	*T*/°C	τ/h	Compoisition of the reaction mixture[b] (%)					
				1a	**A**	**4a**	**5**	**E**	Miscellaneous components
1	EtOH	25	720	11	1	50	2	21	15
2	1,4-Dioxane	25	720	16	4	48	6	22	4
3	Solvent-free	25	720	8	1	41	9	21	20
4	1,4-Dioxane	100	8	—	1	42	22	16	19
5	EtOH	78	8	5	1	47	4	33	10
6	1,4-Dioxane	80	8	2	2	53	20	11	12
7	DCE	80	8	4	3	53	20	12	8
8[c]	1,4-Dioxane	60	15	3 (3)	2 (2)	67 (14)	13 (43)	9 (15)	5 (23)
9	DCE	60	18	8	6	58	12	11	5

[a] Conditions: **1a** (1 mmol), **2a** (1 mmol), NH_4OAc (1 mmol), solvent (2 mL).
[b] ^{19}F NMR spectroscopic data: δ_F 88.50 (**1a**), 81.94 (**A**), 92.72 (**E**).
[c] The results of the experiment using 2 mmol of **1a** are given in parentheses.

tained in the highest yield, with the minimum amount of enamine **E** as the by-product, which was previously obtained in the reaction of ester **1a** with ammonia.[54] The use of a twofold excess of keto ester **1a** in the reaction with acetone **2a** and ammonium acetate allowed the synthesis of pyridone **5** (see Table 1, run *8*).

A large series of three-component reactions of 3-polyfluoroalkyl-3-oxopropanoates **1a—d** and ammonium acetate with methyl ketones **2a—k** were performed under the optimal conditions, resulting in the preparation of a series of 4-(polyfluoroalkyl)pyridin-2-ones **4a—q** in 23—81% yields (Scheme 3, method *C*). However, the reaction with butan-2-one **2b** afforded, apart from pyridone **4b**, a small amount of 5,6-dimethyl-substituted heterocycle **6** (method *C*) that formed through the addition of the methylene group of the ethyl substituent to the trifluoroacyl moiety. This reaction in ethanol allowed us to isolate product **6** in 19% yield (method *D*).

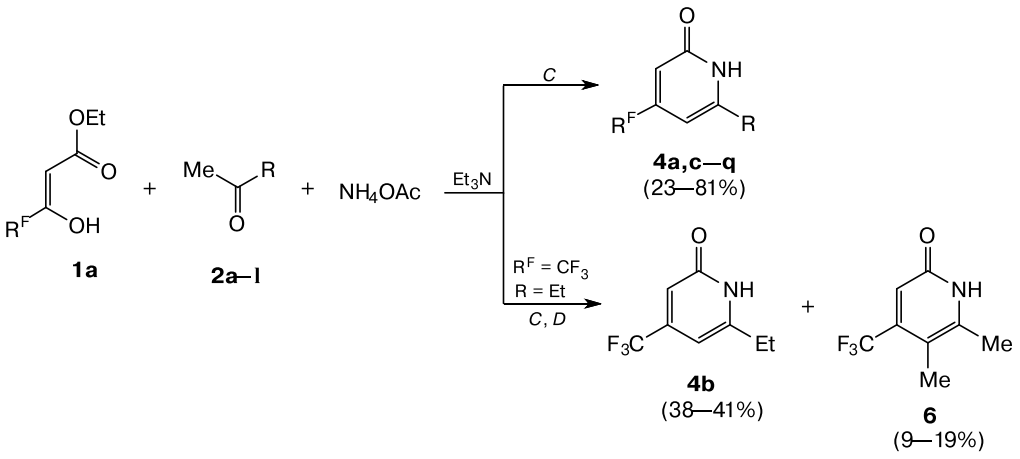
It is worth noting that the reactions with alkyl methyl ketones **2a—e** occur more slowly and afford the target products in lower yields compared to the reactions with (het)aryl methyl ketones **2f—l**. Besides, products **4a—d,m,n,p** were purified by column chromatography, which also led to a decrease in their yield. By contrast, the reactions with (het)aryl methyl ketones **2f—l** occurred at a high rate and were more efficient. Besides, products **4e—l,o,q** precipitated, which accelerated the conversion of the starting reagents.

We also studied the transformations of 3-oxo esters **1b—d** bearing a longer polyfluorinated substituent with ammonium acetate and acetone **2a** or 2-acetylfuran **2i** (see Scheme 3, method *C*). It was found that an increase in the length of the fluorinated substituent leads to a decrease in the yield of pyridinones **4m—q**. Nevertheless, the trends observed in the reactions of trifluoroacetoacetate **1a** are retained. Thus, the yields of pyridones **4n,o,q** derived from 2-acetylfuran **2i** were somewhat higher compared to analogs **4m,p** synthesized from acetone **2a**.

The reaction using a twofold excess of keto ester **1a** with acetone **2a** and ammonium acetate enabled us to prepare compound **5** (see Table 1, run *8*). Evidently, this compound is the product of further transformations of pyridone **4a** in the presence of keto ester **1a**. Actually, the methyl group of pyridone **4a** can easily bind to the trifluoroacetyl moiety of compound **1a** in the presence of proline, which efficiently catalyzes the aldolyzation (Scheme 4).

The structures of pyridinones **3—6** were confirmed by IR spectroscopy, ^{1}H, ^{19}F, and ^{13}C NMR spectro-

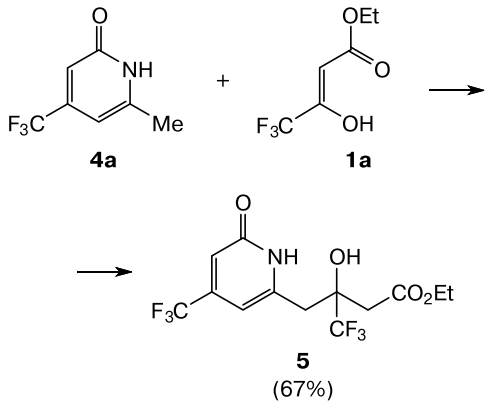
Scheme 3



Starting compounds				Products	Yield
1	R^F	**2**	R		(%)
1a	CF_3	**2a**	Me	**4a**	63
	CF_3	**2b**	Et	**4b**, **6**	
	CF_3	**2c**	Bu	**4c**	57
	CF_3	**2d**	Pr^i	**4d**	49
	CF_3	**2e**	Bu^t	**4e**	37
	CF_3	**2f**	Ph	**4f**	81
	CF_3	**2g**	4-MeC_6H_4	**4g**	69
	CF_3	**2h**	2,4-$Me_2C_6H_3$	**4h**	64
	CF_3	**2i**	Furan-2-yl	**4i**	76
1a	CF_3	**2j**	Thiophen-2-yl	**4f**	54
	CF_3	**2k**	Pyridin-2-yl	**4k**	72
	CF_3	**2l**	Pyridin-4-yl	**4l**	48
1b	$H(CF_2)_2$	**2a**	Me	**4m**	31
	$H(CF_2)_2$	**2i**	Furan-2-yl	**4n**	43
1c	C_2F_5	**2i**	Furan-2-yl	**4o**	27
1d	C_3F_7	**2a**	Me	**4p**	23
	C_3F_7	**2i**	Furan-2-yl	**4q**	36

Reagents and conditions: method *C*: 1,4-dioxane, 60 °C; method *D*: EtOH, 60 °C.

Scheme 4

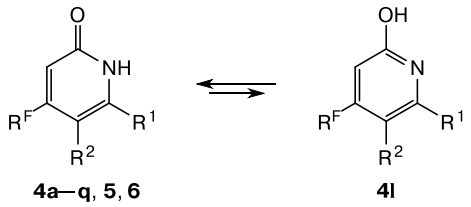


Reagents and conditions: 1a (1 equiv.), 1,4-dioxane, L-proline, 80 °C.

scopy, high-resolution mass spectrometry, and elemental analysis. Particular attention was given to the lactam—lactim tautomerism typical of pyridin-2-ones.[2,23] It was noted[55] that the lactam form predominates both in the solid state and in solution although it can be transformed into the lactim form depending on the solvent and the electronic nature of the substituents of the heterocycle.

The ^{13}C NMR spectroscopic data do not allow the discrimination between the tautomeric forms of compounds **4a—q**, **5**, and **6** because, in all cases, the carbon atom C(2) resonates at δ 161—163, which is characteristic of the sp^2-hybridized carbon atom of both the amide and imine forms. The tautomeric structures of heterocycles **4a—l, 5**, and **6** were determined from the IR spectra recorded for the solid state and solutions. According to the IR spectra of the solid samples, pyridin-2-ones **4a—k,m—q**, **5**, and **6** exist in the lactam form (Scheme 5) because their spectra show absorption bands of C=O stretching vibrations at ν 1645—1672 cm^{-1} characteristic of the carbonyl group involved in intermolecular hydrogen bonding.[56] The exception is 4-pyridinyl-substituted pyridine **4l**, which exists in the lactim form in the solid state, because the IR spectrum of **4l** has no absorption of the C=O group but shows broadened absorption bands of the OH group at 2506 cm^{-1}. However, the IR spectrum of **4l** in weakly polar chloroform demonstrated structural changes, as evidenced by an absorption band at 1673 cm^{-1} assigned to C=O vibrations of the amide function. The IR spectra of **4a—d,k** in solution (MeCN or $CHCl_3$) show C=O absorption bands at 1678—1683 cm^{-1} like the spectra of the solid samples. Therefore, our study demonstrated that the lactam—lactim tautomerism is characteristic only of pyridin-4-yl-substituted pyridone **4l** (Scheme 5).

Scheme 5



Pyridones **4f** and **4l** were studied by X-ray diffraction, which confirmed that compounds **4f** and **4l** were 6-phenyl-4-(trifluoromethyl)pyridin-2(1*H*)-one and 4-trifluoromethyl[2,4′-bipyridin]-6-ol, respectively (Fig. 1).

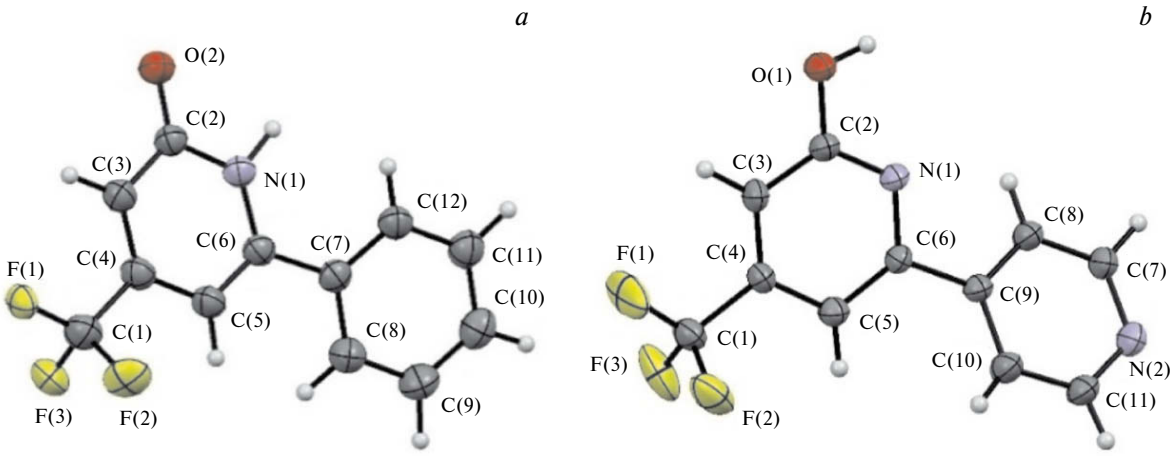


Fig. 1. X-ray molecular structures of pyridones **4f** (*a*) and **4l** (*b*).

The crystal packing of **4f** consists of dimers linked by the intermolecular N(1)—H(1)···O(2) hydrogen bond (1.859 Å, Fig. 2); the crystal packing of **4l** is formed by chains of molecules connected by the intermolecular O(1)—H(1)···N(2) hydrogen bond (1.827 Å, Fig. 3).

The use aqueous ammonia, which slowed down the formation of target pyridones **3** and **4**, allowed us to propose the mechanism for the formation of the reaction products (Scheme 6). Apparently, the first step of the reaction involves the aldol addition of methyl ketones **2** at the polyfluoroacyl substituent of keto esters **1** to form aldols **A**.

Ammonia acts as the base that catalyzes the aldol addition. Therefore, these reactions can be considered as autocatalytic. Then ammonia can react with aldols **A** through two equally probable pathways: at the ethoxycarbonyl group to from amides **X1** or at the keto group to form amines **X2** (see Scheme 6). Both these intermediates can undergo intramolecular cyclization to dihydropyridin-2-ones **3**. The dehydration of the latter affords pyridones **4**. Besides, the side condensation reaction of ester **1** with ammonia generates enamine **E**. It should be noted that if enamines **E** were intermediates in these transformations, the reactions would give isomeric 2-(polyfluoroalkyl)pyridin-4-ones rather than 4-(polyfluoroalkyl)pyridin-2-ones, but it was not the case.

Taking into account the great potential of pyridin-2-ones as biologically active compounds, we evaluated the synthesized trifluoromethylated representatives for selected biological activities. First, we focused on the antimycotic properties because the known synthetic antifungal agent ciclopirox was designed based on pyridin-2-ones.[22] Pyridones **4a—d,f,g,i—j,l** and **6** were evaluated for antifungal activity according to a known procedure[53,57] against seven pathogenic fungal strains (*in vitro*): *T. mentagrophytes var. interdigitale* (RCPF (Russian Collection of Pathogenic Fungi) F-1459/11044), *T. tonsurans* (RCPF F-1396/228), *E. floccosum* (RCPF F-1659/17), *M. canis* (RCPF F-1643/1585), *C. albicans* (RCPF Y-401/NCTC 885-653), *T. rubrum* (RCPF F-1408), and *C. parapsilosis* (RCPF 1245/ATCC 22019). The minimum inhibitory concentrations (MIC), at

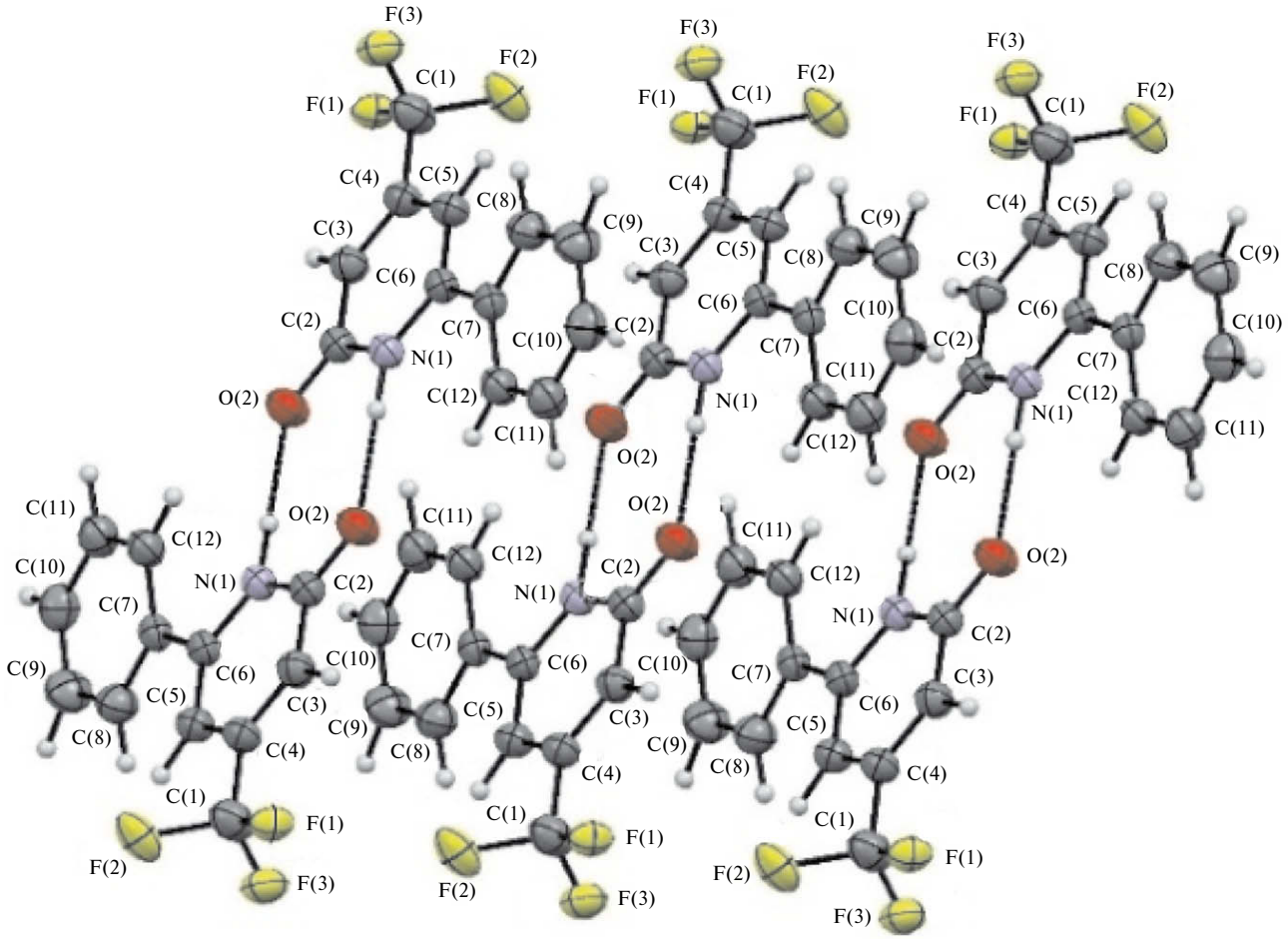


Fig. 2. X-ray crystal packing of pyridone **4f**.

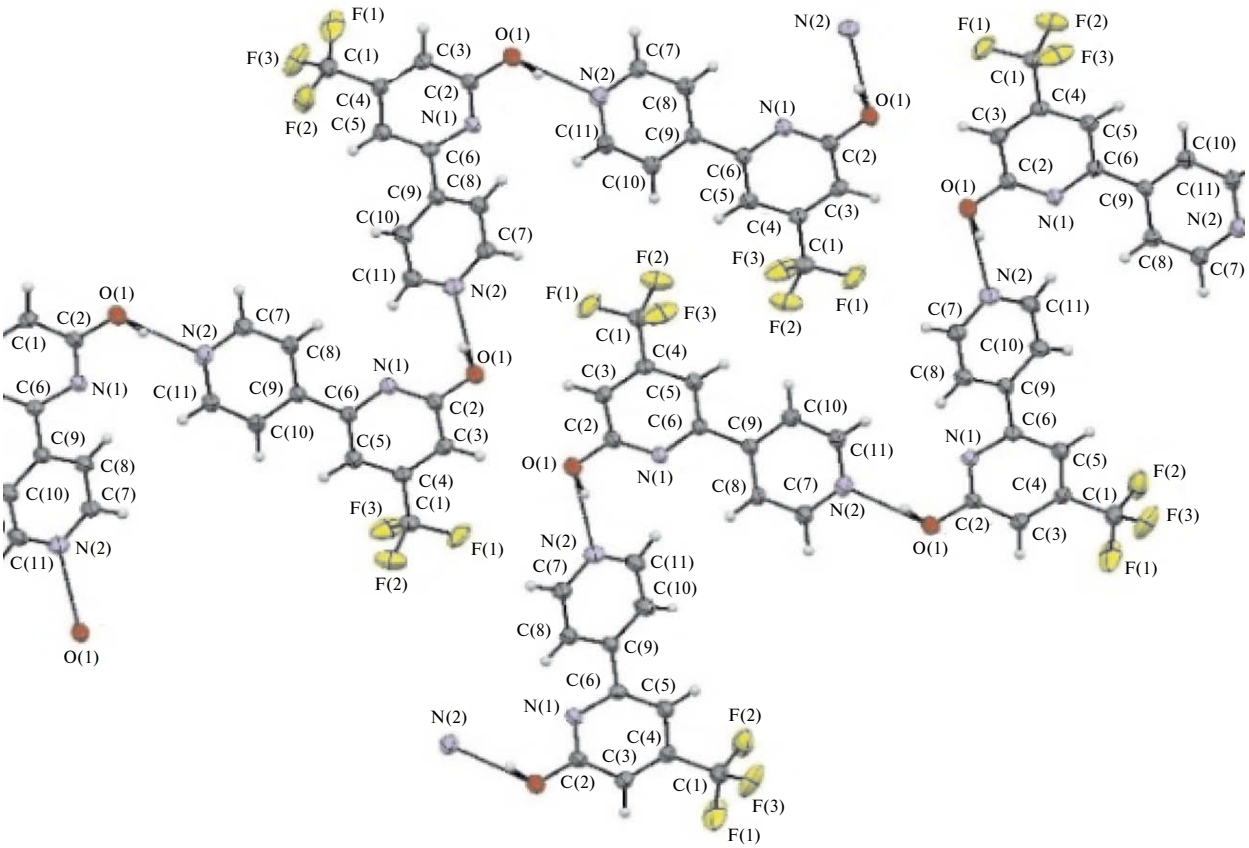


Fig. 3. X-ray crystal packing of pyridone **4l**.

Scheme 6

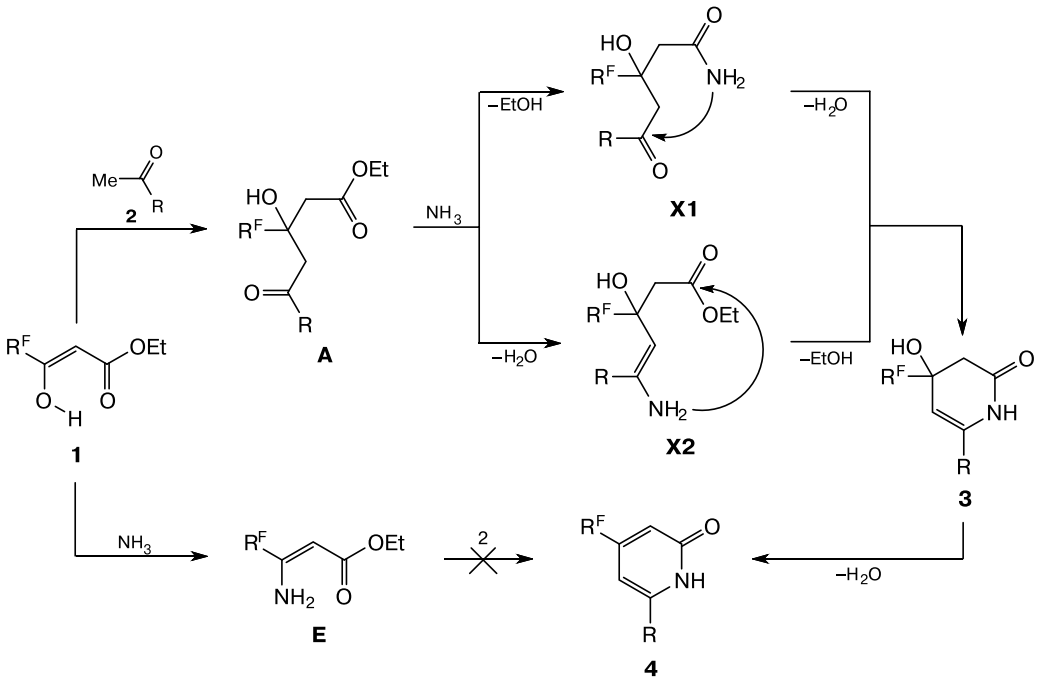


Table 2. Acute toxicity and analgesic activity of compounds of series **4**

Compound	Dose /mg kg^{-1}	Analgesic activity [a] (%)		Acute toxicity evaluation	
		1 h	2 h	Dose /mg kg^{-1}	Survived mice (%)
4a	15	H.a[b]	72 (0.005)	300	100
4c	15	40 (0.004)	H.a[b]	300	100
4f	15	29 (0.016)	53 (0.050)	300	100
4i	15	55 (0.045)	53 (0.012)	150	100
4l	15	75 (0.00003)	53 (0.009)	300	100
Diclofenac	10	69.7±5.2[c]	67.7±10.1[c]	100	66.7

[a] An increase in the nociceptive response: % compared to the control group (p compared to the control group).
[b] Non-active, $p > 0.1$.
[c] The average of three independent experiments ±SEM.

which the growth of pathogenic fungi was inhibited, were determined using fluconazole as the positive control. 6-Furanylpyridin-2-one **4i** showed weak inhibitory activity (MIC 50 μg mL^{-1}) against the strain *T. interdigitale*, and its thiophene and tolyl analogs **4g,j** exhibited weak activity against the strain *E. floccosum* (MIC 50 μg mL^{-1}). 6-Phenylpyridin-2-one **4f** showed moderate inhibitory activity (MIC 25 μg mL^{-1}) against the strains *T. tonsurans* and *E. floccosum*.

The antibacterial activity was evaluated *in vitro* against the Gram-negative bacteria *Neisseria gonorrhoeae* (NCTC 12700). The clinical drug spectinomycin was used as the positive control. Pyridinones **4d** (R = Pr^{i}), **4l** (R is pyridin-4-yl), and **6** showed weak antibacterial activity (MIC 62.5 μg mL^{-1}), compound **4c** (R = Bu) exhibited moderate activity (MIC 7.8 μg mL^{-1}), and the highest antibacterial activity was observed for ethyl-containing pyridone **4b** (MIC 1.9 μg mL^{-1}).

According to the literature data, the pyridin-2-one moiety is an appropriate structural scaffold for the synthesis of cannabinoid CB2 receptor ligands promising for the design of analgesics.[58—60] Besides, the antiepileptic agent perampanel exhibited significant analgesic activity in a series of acute and chronic pain tests.[61]

We tested the analgesic effect and acute toxicity of pyridones **4a,c,f,i,l** in *in vivo* experiments. The acute toxicity was evaluated in CD-1 mice by the intraperitoneal route. The analgesic activity was assessed at a dose of 15 mg kg^{-1} (intraperitoneal administration) using the hot-plate test in SD rats.[62,63] The response of animals to the nociceptive stimulus was recorded 1 and 2 h after the administration of the tested compounds (Table 2). Diclofenac at a dose of 10 mg kg^{-1} was used as the reference agent.

It was demonstrated that all the tested compounds were non-toxic at a dose of 150—300 mg kg^{-1} and exhibited the antinociceptive effect to a certain degree. The analgesic activity of alkyl- and phenyl-containing pyridones **4a,c,f** proved to be lower than that of hetaryl-substituted analogs **4i,l** (see Table 2). The highest antinociceptive effect was observed for 6-(pyridin-4-yl) pyridin-2-one **4l** over the first hour of measurements (75%), which was comparable with that of diclofenac. However, the activity decreased to 53% during the second hour. The structure—activity relationship demonstrates that the introduction of different heteroatom-containing substituents at the C(6) position is promising for the further structural optimization.

In summary, we developed a new facile one-pot three-component synthesis of 4-trifluoromethylpyridin-2-ones and their polyfluoroalkyl-substituted analogs based on the reactions of commercially available 3-oxo esters, methyl ketones, and ammonium acetate. The new method satisfies the green chemistry principles and has good variability. Thus, the new method allows the variation of the fluorinated substituent at the C(4) position in the newly formed pyridone ring and the introduction of different alkyl, aryl, or hetaryl substituents at the C(6) position, leaving the C(3) and C(5) positions of the heterocycle accessible for subsequent modifications in CH-functionalization reactions. This may be useful for the synthesis of new biologically active compounds. The prospects of the synthesized pyridones in this field are evidenced by the moderate antimycotic, high antibacterial, and significant analgesic activity of the synthesized pyridones.

Experimental

The melting points were determined in open capillary tubes using a Stuart SMP30 melting point apparatus. The IR spectra of solid samples were measured on a Perkin-Elmer

Spectrum Two Fourier-transform infrared spectrometer equipped with an attenuated total reflectance (ATR) diamond crystal accessory in a region of 400—4000 cm^{-1}; the IR spectra of solutions ($CHCl_3$, MeCN) were recorded on a Perkin-Elmer Spectrum One Fourier-transform infrared spectrometer. The ^1H, ^{19}F, and ^{13}C NMR spectra were recorded in DMSO-d_6 on Bruker AVANCE 500 and Bruker AVANCE DRX-400 spectrometers with Me_4Si (^1H) and C_6F_6 (^{19}F) as the internal standards. The ^{13}C NMR chemical shifts were calibrated using the signal of DMSO-d_6 (δ_C 39.5). The high-resolution ESI mass spectra were measured on a Bruker maXis mass spectrometer. Elemental analysis was performed on a Perkin Elmer 2400 Series II CHN analyzer. Gas-chromatography mass spectra of the reaction mixtures were recorded on a Shimadzu GCMS QP2020 gas chromatograph-mass spectrometer. Column chromatography was carried out on Merck 60 silica gel (0.063—0.200 mm). The following commercially available reagents (Alfa Aesar, Acros Organics, and Sigma—Aldrich) were used: ethyl 4,4,4-trifluoroacetoacetate (**1a**), acetone (**2a**), butan-2-one (**2b**), hexan-2-one (**2c**), 3-methylbutan-2-one (**2d**), 3,3-dimethylbutan-2-one (**2e**), acetophenone (**2f**), 4-methylacetophenone (**2g**), 2,4-dimethylacetophenone (**2h**), 2-acetylfuran (**2i**), 2-acetylthiophene (**2j**), 2-acetylpyridine (**2k**), 4-acetylpyridine (**2l**), aqueous ammonia, and ammonium acetate. Polyfluoroalkyl-3-oxopropanoates **1b—d** were synthesized according to procedures described in the literature.[6] The single-crystal X-ray diffraction data sets for compounds **4f,l** were collected on a Xcalibur 3 diffractometer at 295 (2) K (Mo-Kα radiation, graphite monochromator, CCD detector). The crystal structures were solved by direct methods and refined by the full-matrix least-squares method with anisotropic displacement parameters for all nonhydrogen atoms using the SHELXL-97 program suite.[66,67] The positions of hydrogen atoms were found in difference electron density maps and refined isotropically.

Single crystals of **4f** were obtained by the crystallization from acetonitrile, $C_{11}H_7F_3N_2O$, M = 240.19, orthorhombic crystal system, space group *Pbca*, a = 12.761(2) Å, b = 7.4105(12) Å, c = 22.239(3) Å, α = β = γ = 90°, V = 2103.0(6) $Å^3$, Z = 8, d_{calc} = 1.517 g cm^{-3}, μ(Mo-Kα) = = 0.136 cm^{-1}, F(000) = 976.0. A total of 7760 reflections were collected, of which 2786 reflections are unique (R_{int} = 0.0819) and 1001 reflection are with $I \geqslant 2\sigma(I)$, R_1 = 0.0691, wR_2 = 0.1452, and GOOF = 0.939.

Single crystals of **4l** were obtained by the crystallization from acetonitrile, $C_{12}H_8F_3NO$, M = 239.19, monoclinic crystal system, space group *I2/a*, a = 16.747(3) Å, b = 4.8416(6) Å, c = 25.872(3) Å, α = 90°, β = 91.928(13)°, γ = 90°, V = 2096.6(5) $Å^3$, Z = 8, d_{calc} = 1.516 g cm^{-3}, μ(Mo-Kα) = 0.133 cm^{-1}, F(000) = 976.0. A total of 6049 reflections were collected, of which 2854 reflections are unique (R_{int} = 0.0531) and 1137 reflections are with $I \geqslant 2\sigma(I)$, R_1 = 0.05821, wR_2 = 0.1297, and GOOF = 0.978.

Complete crystallographic data for compounds **4f** and **4l** were deposited with the Cambridge Crystallographic Data Centre (CCDC 2169119 and CCDC 2169120, respectively) and are available, free of charge, at http://www.ccdc.cam.ac.uk/conts/retrieving.html (12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Synthesis of dihydropyridin-2-ones 3 and 4 (general procedure). Method *A*. A mixture of ethyl 4,4,4-trifluoroacetoacetate **1a** (920 mg, 5 mmol) and methyl ketone **2** (5 mmol) in 1,4-dioxane (5 mL) was placed in a 30 mL septum-sealed screw cap vial. Then aqueous ammonia (340 mg, 20 mmol) was added, and the reaction mixture was magnetically stirred with heating to 60 °C for 10—12 h. The progress of the reaction was monitored by TLC and ^{19}F NMR spectroscopy. Then the reaction mixture was concentrated and stored in a Petri dish for 3—7 days until the formation of a crystalline precipitate. The precipitate was triturated with Et_2O, filtered off, recrystallized from acetonitrile, and dried in a drying oven.

Dehydration of dihydropyridin-2-ones 3. Method *B*. A mixture of hydroxydihydropyridone **3a—c** (1 mmol) and *p*-toluenesulfonic acid (247 mg, 1.3 mmol) in toluene (30 mL) was placed in a round-bottom flask. The reaction mixture was refluxed for 6—7 h. The progress of the reaction was monitored by TLC. Then the solvent was removed in a rotary evaporator, and the residue was purified by column chromatography using chloroform as the eluent.

Synthesis of pyridin-2-ones 4. Method *C*. A mixture of keto ester **1** (5 mmol) and methyl ketone **2** (5 mmol) in 1,4-dioxane (5 mL) was placed in a 30 mL septum-sealed screw cap vial. Then ammonium acetate (385 mg, 5 mmol) and triethylamine (505 mg, 5 mmol) were added. The reaction mixture was magnetically stirred with heating to 60 °C for 15—18 h. The progress of the reaction was monitored by TLC and ^{19}F NMR spectroscopy. After completion of the reaction, in the case of products **4a—d,m,n,p** the solvent was removed by evaporation, and the resulting mixture was purified by column chromatography using the appropriate eluent (chloroform, dichloromethane, ethyl acetate). The precipitate that formed in the reaction mixture in the case of products **4e—l,o,q** was filtered off, recrystallized from an appropriate solvent (acetonitrile, ethanol), and dried in a drying oven.

Synthesis of 6-ethyl-4-(trifluoromethyl)pyridin-2(1*H*)-one (4b) and 5,6-dimethyl-4-(trifluoromethyl)pyridin-2(1*H*)-one (6). Method *D*. A mixture of keto ester **1** (920 mg, 5 mmol) and butan-2-one **2** (360 mg, 5 mmol) in ethanol (3 mL) was placed in a septum-sealed screw cap vial. Then ammonium acetate (385 mg, 5 mmol) and triethylamine (505 mg, 5 mmol) were added. The reaction mixture was magnetically stirred with heating to 60 °C for 15 h. The progress of the reaction was monitored by TLC and ^{19}F NMR spectroscopy. Then the solvent was removed in a rotary evaporator, and the residue was purified by column chromatography using chloroform as the eluent.

4-Hydroxy-6-methyl-4-trifluoromethyl-3,4-dihydropyridin-2(1*H*)-one (3a) (with a 7% impurity of 4a) was synthesized by the method *A*. The yield was 263 mg (27%), white powder, m.p. 189—191 °C (acetonitrile). IR, ν/cm^{-1}: 3330, 3222, 3159 (N—H, O—H), 2959, 2919 (C—H), 1652 (C=O), 1171—1079 (C—F). ^1H NMR, δ: 1.79 (s, 3 H, Me); 2.46 (d, 1 H, C(3)H_B, overlapped with DMSO); 2.67 (d, 1 H, C(3)H_A, J = 16.6 Hz); 4.78 (s, 1 H, OH); 6.25 (s, 1 H, C(5)H);

9.59 (s, 1 H, NH). ^{19}F NMR, δ: 80.74 (s, CF_3). Found (%): C, 42.99; H, 4.12; N, 7.16. $C_7H_8F_3NO_2$. Calculated (%): C, 43.09; H, 4.13; N, 7.18.

6-Ethyl-4-hydroxy-4-trifluoromethyl-3,4-dihydropyridin-2(1*H*)-one (3b) (with a 5% impurity of 4b) was synthesized by the method *A*. The yield was 219 mg (21%), white powder, m.p. 153—155 °C (acetonitrile). IR, ν/cm^{-1}: 3332, 3216, 3155 (N—H, O—H), 2996, 2948 (C—H), 1650 (C=O), 1155—1087 (C—F). ^{1}H NMR, δ: 1.03 (t, 3 H, Me, J = 7.5 Hz); 2.09 (q, 2 H, H_2C_{Et}, J = 7.5 Hz); 2.47 (d, 1 H, C(3)H_B, overlapped with DMSO); 2.68 (d, 1 H, C(3)H_A, J = 16.6 Hz); 4.76 (s, 1 H, OH); 6.25 (s, 1 H, C(5)H); 9.57 (s, 1 H, NH). ^{19}F NMR, δ: 80.74 (s, CF_3). Found (%): C, 45.80; H, 4.81; N, 6.68. $C_8H_{10}F_3NO_2$. Calculated (%): C, 45.94; H, 4.82; N, 6.70.

6-Butyl-4-hydroxy-4-trifluoromethyl-3,4-dihydropyridin-2(1*H*)-one (3c) (with a 10% impurity of 4c) was synthesized by the method *A*. The yield was 355 mg (30%), white powder, m.p. 169—171 °C (acetonitrile). IR, ν/cm^{-1}: 3348, 3221, 3154 (N—H, O—H), 2960—2875 (C—H), 1647 (C=O), 1177—1083 (C—F). ^{1}H NMR, δ: 0.87 (t, 3 H, Me, J = 7.2 Hz); 1.29 (m, 2 H, H_2C_{Bu}); 1.43 (m, 2 H, H_2C_{Bu}); 2.07 (m, 2 H, H_2C_{Bu}); 2.47 (d, 1 H, C(3)H_B, overlapped with DMSO); 2.67 (d, 1 H, C(3)H_A, J = 16.6 Hz); 4.75 (s, 1 H, OH); 6.24 (s, 1 H, C(5)H); 9.54 (s, 1 H, NH). ^{19}F NMR, δ: 80.67 (s, CF_3). Found (%): C, 50.59; H, 5.93; N, 5.80. $C_{10}H_{14}F_3NO_2$. Calculated (%): C, 50.63; H, 5.95; N, 5.90.

6-Methyl-4-(trifluoromethyl)pyridin-2(1*H*)-one (4a) was synthesized by the method *B*, the yield was 133 mg (75%), and the method *C*, the yield was 557 mg (63%), colorless crystals, m.p. 123—125 °C (chloroform as the eluent). Previously, compound **4a** was synthesized and characterized in the study,[68] in which the spectroscopic data were not reported, and the melting point (133.8—135.2 °C) is inconsistent with our data. IR, ν/cm^{-1}: 3123 (N—H), 2924—2782 (C—H), 1669 (C=O), 1636 (C=C), 1168—1083 (C—F). IR, ν/cm^{-1}:1673 (C=O), 1638 (C=C). ^{1}H NMR, δ: 2.24 (s, 3 H, Me); 6.25 (s, 1 H, C(5)H); 6.47 (s, 1 H, C(3)H); 12.19 (br.s, 1 H, NH). ^{13}C NMR, δ: 18.7 (Mm); 98.7 (C(5)); 113.6 (C(3)); 122.5 (q, CF_3, J = 274.4 Hz); 140.8 (q, C(4), J = 31.9 Hz); 149.1 (C(6)), 162.6 (C(2)). ^{19}F NMR, δ: 97.13 (s, CF_3). MS: found m/z 178.0474 $[M + H]^+$; calculated for $C_7H_7F_3NO$ 178.0474. Found (%): C, 47.72; H, 3.45; N, 7.81. $C_7H_6F_3NO$. Calculated (%): C, 47.47; H, 3.41; N, 7.91.

6-Ethyl-4-(trifluoromethyl)pyridin-2(1*H*)-one (4b) was synthesized by the method *B*, the yield was 136 mg (71%), the method *C*, the yield was 391 mg (41%), and the method *D*, the yield was 363 mg (38%), milky white powder, m.p. 70—72 °C (chloroform as the eluent). IR, ν/cm^{-1}: 3128 (N—H), 2926—2855 (C—H), 1667 (C=O), 1631 (C=C), 1177—1072 (C—F). IR, ν/cm^{-1}:1680 (C=O), 1630 (C=C). ^{1}H NMR, δ: 1.17 (s, 3 H, Me_{Et}, J = 7.5 Hz); 2.54 (q, 2 H, H_2C_{Et}, J = 7.5 Hz); 6.24 (br.s, 1 H, C(5)H); 6.50 (s, 1 H, C(3)H); 12.18 (br.s, 1 H, NH). ^{13}C NMR, δ: 12.7 (Me_{Et}); 25.7 (H_2C_{Et}); 97.2 (C(5)); 114.0 (C(3)); 122.6 (q, CF_3, J = 274.4 Hz); 140.9 (q, C(4), J = 32.0 Hz); 154.4 (C(6)); 162.2 (C(2)). ^{19}F NMR., δ: 97.24 (s, CF_3). MS: found m/z 214.0449 $[M + Na]^+$; calculated for $C_8H_8F_3NNaO$ 214.0450. Found (%): C, 50.73; H, 4.33; N, 7.23. $C_7H_6F_3NO$. Calculated (%): C, 50.27; H, 4.22; N, 7.33.

6-Butyl-4-(trifluoromethyl)pyridin-2(1*H*)-one (4c) was synthesized by the method *B*, the yield was 149 mg (68%), and the method *C*, the yield was 624 mg (57%), colorless crystals, m.p. 76—77 °C (chloroform as the eluent). IR, ν/cm^{-1}: 3130 (N—H), 2963—2872 (C—H), 1668 (C=O), 1628 (C=C), 1177—1082 (C—F). IR (MeCN), ν/cm^{-1}:1680 (C=O), 1627 (C=C). ^{1}H NMR, δ: 0.89 (s, 3 H, Me); 1.25—1.32 (m, 2 H, H_2C_{Bu}); 1.53—1.60 (m, 2 H, H_2C_{Bu}); 2.52 (t, 2 H, H_2C_{Bu}, J = 7.8 Hz, overlapped with DMSO); 6.24 (br.s, 1 H, C(5)H); 6.49 (s, 1 H, C(3)H); 12.18 (br.s, 1 H, NH). ^{13}C NMR, δ: 13.5 (Me_{Bu}); 21.5 (γ-H_2C_{Bu}); 30.2 (β-H_2C_{Bu}); 32.0 (α-H_2C_{Bu}); 98.1 (C(5)), 113.9 (C(3)), 122.5 (q, CF_3, J = 274.0 Hz); 140.8 (q, C(4), J = 32.0 Hz); 153.1 (C(6)); 162.2 (C(2)). ^{19}F NMR, δ: 97.24 (s, CF_3). MS: found m/z 220.0944 $[M + H]^+$; calculated for $C_{10}H_{13}F_3NO$ 220.0944. Found (%): C, 54.96; H, 5.66; N, 6.33. $C_{10}H_{12}F_3NO$. Calculated (%): C, 54.79; H, 5.52; N, 6.39.

6-(Propan-2-yl)-4-(trifluoromethyl)pyridin-2(1*H*)-one (4d) was synthesized by the method *C*, the yield was 502 mg (49%), colorless crystals, m.p. 100—103 °C (chloroform as the eluent). IR, ν/cm^{-1}: 3124 (N—H), 2972—2881 (C—H), 1666 (C=O), 1628 (C=C), 1208—1066 (C—F). IR (MeCN), ν/cm^{-1}: 1683 (C=O), 1628 (C=C). ^{1}H NMR, δ: 1.19, 1.20 (both s, 3 H each, 2 Me); 2.80—2.88 (m, 1 H, C<u>H</u>Me_2); 6.20 (br.s, 1 H, C(5)H); 6.51 (s, 1 H, C(3)H); 12.15 (br.s, 1 H, NH). ^{13}C NMR, δ: 21.0 (2 Me); 31.6 (<u>CH</u>Me_2); 95.3 (C(5)); 114.3 (C(3)); 122.6 (q, CF_3, J = 274.4 Hz); 140.9 (q, C(4), J = 32.4 Hz); 158.4 (C(6)); 162.2 (C(2)). ^{19}F NMR, δ: 97.29 (s, CF_3). MS: found m/z 206.0783 $[M + H]^+$; calculated for $C_9H_{11}F_3NO$ 206.0787. Found (%): C, 52.76; H, 5.17; N, 6.89. $C_9H_{10}F_3NO$. Calculated (%): C, 52.68; H, 4.91; N, 6.83.

6-*tert*-Butyl-4-(trifluoromethyl)pyridin-2(1*H*)-one (4e) was synthesized by the method *B*, the yield was 405 mg (37%), colorless crystals, m.p. 172—174 °C (acetonitrile). IR, ν/cm^{-1}: 3133 (N—H), 2974—2877 (C—H), 1671 (C=O), 1615 (C=C), 1183—1084 (C—F). ^{1}H NMR, δ: 1.28 (s, 9 H, 3 Me); 6.11 (br.s, 1 H, C(5)H); 6.55 (br.s, 1 H, C(3)H); 11.91 (br.s, 1 H, NH). ^{13}C NMR, δ: 28.3 (3 Me); 35.2 (<u>C</u>Me_3); 94.7 (C(5)); 114.5 (C(3)); 122.6 (q, CF_3, J = 274.2 Hz); 140.6 (q, C(4), J = 32.2 Hz); 160.0 (C(6)); 162.5 (C(2)). ^{19}F NMR, δ: 97.21 (s, CF_3). MS: found m/z 220.0941 $[M + H]^+$; calculated for $C_{10}H_{13}F_3NO$ 220.0944. Found (%): C, 54.52; H, 5.68; N, 6.47. $C_{10}H_{12}F_3NO$. Calculated (%): C, 54.79; H, 5.52; N, 6.39.

6-Phenyl-4-(trifluoromethyl)pyridin-2(1*H*)-one (4f) was synthesized by the methods *A*, the yield was 514 mg (43%), and method *C*, the yield was 968 mg (81%), white powder, m.p. 188—189 °C (ethanol). The physicochemical characteristics are consistent with the literature data.[69]

6-(4-Methylphenyl)-4-(trifluoromethyl)pyridin-2(1*H*)-one (4g) was synthesized by the method *A*, the yield was 455 mg (36%), and the method *C*, the yield was 873 mg (69%), white powder, m.p. 247—249 °C (ethanol). The physicochemical characteristics are consistent with the literature data, m.p. was not reported.[69]

6-(2,4-Dimethylphenyl)-4-(trifluoromethyl)pyridin-2(1*H*)-one (4h) was synthesized by the method *A*, the yield was 427 mg (32%), and the method *C*, the yield was 854 mg (64%), yellow powder, m.p. 144—145 °C (acetonitrile). IR, ν/cm^{-1}: 3105 (N—H), 2951—2871 (C—H), 1672 (C=O), 1615 (C=C), 1193—1070 (C—F). ^{1}H NMR, δ: 2.25 (s, 3 H, *p*-Me); 2.32 (s, 3 H, *o*-Me); 6.33 (br.s, 1 H, C(5)H); 6.69 (s, 1 H, C(3)H); 7.10—7.15 (m, 2 H, CH_{Ph}); 7.23—7.24 (m, 1 H, CH_{Ph}); 12.30 (br.s, 1 H, NH). ^{13}C NMR, δ: 19.4 (*p*-Me); 20.7 (*o*-Me); 100.9 (C(5)); 114.5 (C(3)); 124.5 (q, CF_3, J = 274.0 Hz); 126.4 (*ipso*-C); 129.2 (*o*-C); 131.1 (*m*-C, *m′*-C); 135.5 (*o′*-C); 139.2 (*p*-C); 140.6 (q, C(4), J = 32.4 Hz); 150.7 (C(6)); 162.1 (C(2)). ^{19}F NMR, δ: 97.44 (s, CF_3). S: found *m/z* 268.0941 $[M + H]^+$; calculated for $C_{14}H_{13}F_3NO$ 268.0944. Found (%): C, 62.85; H, 4.59; N, 5.33. $C_{14}H_{12}F_3NO$. Calculated (%): C, 62.92; H, 4.53; N, 5.24.

6-(Furan-2-yl)-4-(trifluoromethyl)pyridin-2(1*H*)-one (4i) was synthesized by the method *A*, the yield was 447 mg (39%), and the method *C*, the yield was 870 mg (76%), yellow powder, m.p. 191—192 °C (acetonitrile). IR, ν/cm^{-1}: 3112 (N—H), 2934—2809 (C—H), 1670 (C=O), 1625 (C=C), 1172—1078 (C—F). ^{1}H NMR, δ: 6.71—6.72 (m, 2 H, C(5) H, CH_{Fur}); 6.95 (br.s, 1 H, C(3)H); 7.40 (s, 1 H, CH_{Fur}); 7.92 (m, 1 H, CH_{Fur}); 12.23 (br.s, 1 H, NH). ^{13}C NMR, δ: 98.8 (C(5)); 110.3 (C(3)); 111.5 (C(4′)); 112.6 (C(3′)); 122.5 (q, CF_3, J =273.8 Hz); 140.8 (q, C(4), J = 32.8 Hz); 141.9 (C(5′)); 145.6 (C(2′)); 147.6 (C(6)); 162.7 (C(2)). ^{19}F NMR, δ: 97.72 (br.s, CF_3). MS: found *m/z* 230.0426 $[M + H]^+$; calculated for $C_{10}H_7F_3NO_2$ 230.0423. Found (%): C, 52.20; H, 2.53; N, 6.05. $C_{10}H_6F_3NO_2$. Calculated (%): C, 52.41; H, 2.64; N, 6.11.

6-(Thiophen-2-yl)-4-(trifluoromethyl)pyridin-2(1*H*)-one (4j) was synthesized by the method *A*, the yield was 343 mg (28%), and the method *C*, the yield was 662 mg (54%), yellow powder, m.p. 201—202 °C (acetonitrile). The physicochemical characteristics are consistent with the literature data.[69]

4-Trifluoromethyl-2,2′-bipyridin-6(1*H*)-one (4k) was synthesized by the method *C*, the yield was 864 mg (72%), pale yellow powder, m.p. 145—147 °C (acetonitrile). IR, ν/cm^{-1}: 3128 (N—H), 2988—2880 (C—H), 1653 (C=O), 1610 (C=C), 1580 (C=N), 1173—1078 (C—F). IR ($CHCl_3$), ν/cm^{-1}: 1677 (C=O), 1623 (C=C). ^{1}H NMR, δ: 6.93 (s, 1 H, C(5)H); 7.52—7.55 (m, 1 H, C(4′)H); 7.69 (br.s, 1 H, C(3)H); 8.01 (td, 1 H, C(5′)H, J = 7.7 Hz, J = 1.8 Hz); 8.29 (dm, 1 H, C(3′)H, J = 8.0 Hz); 8.72—8.73 (m, 1 H, C(6′)H); 11.83 (br.s, 1 H, NH). ^{13}C NMR, δ: 102.7 (C(5)); 111.7 (C(3)); 121.0 (C(4′), C(5′)); 122.6 (q, CF_3, J = 274.5 Hz); 125.1 (C(3′)); 137.6 (C(6′)); 140.8 (q, C(4), J = 33.1 Hz); 149.5 (C(2′)); 150.6 (C(6)); 162.7 (C(2)). ^{19}F NNMR, δ: 98.09 (s, CF_3). MS: found *m/z* 241.0580 $[M + H]^+$; calculated for $C_{11}H_8F_3N_2O$ 241.0583. Found (%): C, 54.91; H, 3.06; N, 11.74. $C_{11}H_7F_3N_2O$. Calculated (%): C, 55.01; H, 2.94; N, 11.66.

4-Trifluoromethyl-2,4′-bipyridin-6(1*H*)-one (4l) was synthesized by the method *C*, the yield was 576 mg (48%), milky white powder, m.p. 236—238 °C (acetonitrile). IR, ν/cm^{-1}: 3079—2886 (C—H), 2506 (O—H), 1605 (C=C), 1561 (C=N), 1158—1064 (C—F). IR ($CHCl_3$), ν/cm^{-1}:1672 (C=O), 1625 (C=C). ^{1}H NMR, δ: 6.96 (s, 1 H, C(5)H); 7.53 (br.s, 1 H, C(3)H); 7.97—7.98 (m, 2 H, C(3′)H); 8.71—8.72 (m, 2 H, C(2′)H); 12.16 (br.s, 1 H, NH). ^{13}C NMR, δ: 105.0 (C(5)); 110.5 (C(3)); 121.0 (C(3′)); 122.6 (q, CF_3, J = 273.6 Hz); 140.9 (q, C(4), J = 33.0 Hz); 142.2 (C(2′)); 150.3 (C(4′)); 151.1 (C(6)); 163.5 (C(2)). ^{19}F NMR, δ: 98.45 (s, CF_3). MS: found *m/z* 241.0585 $[M + H]^+$; calculated for $C_{11}H_8F_3N_2O$ 241.0583. Found (%): C, 55.10; H, 3.08; N, 11.78. $C_{11}H_7F_3N_2O$. Calculated (%): C, 55.01; H, 2.94; N, 11.66.

6-Methyl-4-(1,1,2,2-tetrafluoroethyl)pyridin-2(1*H*)-one (4m) was synthesized by the method *C*, the yield was 324 mg (31%), white powder, m.p. 121—123 °C (dichloromethane as the eluent). IR, ν/cm^{-1}: 3124 (N—H), 2928—2778 (C—H), 1655 (C=O), 1632 (C=C), 1131—1042 (C—F). ^{1}H NMR, δ: 2.24 (s, 3 H, Me); 6.15 (s, 1 H, C(5)H); 6.36 (s, 1 H, C(3)H); 6.75 (tt, 1 H, $(CF_2)_2H$, J = 52.1 Hz, J = 4.6 Hz); 12.12 (br.s, 1 H, NH). ^{13}C NMR, δ: 18.7 (Me), 99.8 (C(5)), 109.7 (tt, $CF_2\underline{C}F_2H$, J = 249.3 Hz, J = 37.6 Hz); 114.0 (tt, $\underline{C}F_2CF_2H$, J = 249.3 Hz, J = 27.6 Hz); 114.6 (C(3)); 142.1 (t, C(4), J = 24.1 Hz); 148.2 (C(6)); 162.1 (C(2)). ^{19}F NMR, δ: 25.71 (dt, 2 F, $CF_2C\underline{F_2}H$, J = 52.1 Hz, J = 6.1 Hz), 44.92 (s, 2 F, $C\underline{F_2}CF_2H$). MS: found *m/z* 210.0536 $[M + H]^+$; calculated for $C_8H_8F_4NO$ 210.0537. Found (%): C, 45.79; H, 3.63; N, 6.80. $C_8H_7F_4NO$. Calculated (%): C, 45.94; H, 3.37; N, 6.70.

6-(Furan-2-yl)-4-(1,1,2,2-tetrafluoroethyl)pyridin-2(1*H*)-one (4n) was synthesized by the method *C*, the yield was 561 mg (43%), yellow powder, m.p. 168—169 °C (acetonitrile). IR, ν/cm^{-1}: 3121 (N—H), 2934—2804 (C—H), 1645 (C=O), 1625 (C=C), 1131—1080 (C—F). ^{1}H NMR, δ: 6.59 (s, 1 H, C(5)H); 6.70—6.71 (m, 1 H, CH_{Fur}); 6.86 (tt, 1 H, $(CF_2)_2H$, J = 51.8 Hz, J = 4.6 Hz); 6.89 (br.s, 1 H, C(3)H); 7.37 (s, 1 H, CH_{Fur}); 7.91 (m, 1 H, CH_{Fur}); 12.13 (br.s, 1 H, NH). ^{13}C NMR, δ: 99.7 (C(3), C(5)); 109.7 (tt, $CF_2\underline{C}F_2H$, J = 249.5 Hz, J = 37.4 Hz); 111.2 (C(3′)); 112.5 (C(4′)); 114.0 (tt, $\underline{C}F_2CF_2H$, J = 249.5 Hz, J = 27.7 Hz); 141.9 (t, C(4), J = 24.7 Hz); 142.1 (C(5′)); 145.3 (C(2′)); 148.0 (C(6)); 162.6 (C(2)). ^{19}F NMR, δ: 25.60 (dt, 2 F, $CF_2C\underline{F_2}H$, J = 52.0 Hz, J = 5.6 Hz); 44.98 (s, 2 F, CF_2). MS: found *m/z* 262.0483 $[M + H]^+$; calculated for $C_{11}H_8F_4NO_2$ 262.0486. Found (%): C, 50.53; H, 2.69; N, 5.34. $C_{11}H_7F_4NO_2$. Calculated (%): C, 50.59; H, 2.70; N, 5.36.

6-(Furan-2-yl)-4-(pentafluoroethyl)pyridin-2(1*H*)-one (4o) was synthesized by the method *C*, the yield was 376 mg (27%), yellow powder, m.p. 188—190 °C (acetonitrile). IR, ν/cm^{-1}: 3140 (N—H), 2947—2757 (C—H), 1668 (C=O), 1616 (C=C), 1198—1153 (C—F). ^{1}H NMR, δ: 6.69 (s, 1 H, C(5)H); 6.71—6.72 (m, 1 H, CH_{Fur}); 6.92 (br.s, 1 H, C(3)H); 7.40 (s, 1 H, CH_{Fur}); 7.92 (s, 1 H, CH_{Fur}); 12.28 (br.s, 1 H, NH). ^{13}C NMR, δ: 99.72 (C(5)); 111.6 (C(3)); 111.8 (tq, $\underline{C}F_2CF_3$, J = 254.9 Hz, J = 38.2 Hz); 112.6 (C(4′), C(3′)), 118.3 (dt, $CF_2\underline{C}F_3$, J = 286.5 Hz, J = 38.2 Hz); 139.4 (t, C(4), J = 24.1 Hz); 142.8 (C(5′)); 145.5 (C(2′)); 148.0 (C(6)); 162.6 (C(2)). ^{19}F NMR, δ: 45.88 (s, 2 F, $C\underline{F_2}CF_3$); 78.86 (s, 3 F, $C\underline{F_3}$). MS: found *m/z* 280.0393 $[M + H]^+$; calculated for $C_{11}H_7F_5NO_2$ 280.0391. Found (%): C, 47.27; H, 2.21; N, 5.11. $C_{11}H_6F_5NO_2$. Calculated (%): C, 47.33; H, 2.17; N, 5.02.

4-Heptafluoropropyl-6-methylpyridin-2(1*H*)-one (4p) was synthesized by the method *C*, the yield was 319 mg (23%), colorless crystals, m.p. 92—93 °C (ethyl acetate as the eluent). IR, ν/cm^{-1}: 3549 (N—H), 2915—2810 (C—H), 1672 (C=O), 1629 (C=C), 1225—1147 (C—F). ^{1}H NMR, δ: 2.27 (s, 3 H, Me); 6.20 (s, 1 H, C(5)H); 6.43 (s, 1 H, C(3)H); 12.28 (br.s, 1 H, NH). ^{13}C NMR, δ: 18.7 (Me); 99.7 (C(5)); 113.6 (tq, $CF_2\underline{C}F_2CF_3$, J = 265.1 Hz, J = 37.6 Hz); 113.6 (tt, $\underline{C}F_2CF_2CF_3$, J = 256.0 Hz, J = 30.8 Hz); 115.5 (C(3)); 117.3 (qt, CF_3, J = 288.0 Hz, J = 34.1 Hz); 139.7 (t, C(4), J = 23.9 Hz); 148.9 (C(6)); 161.8 (C(2)). ^{19}F NMR, δ: 36.38 (s, 2 F, CF_2); 48.46 (br.d, 2 F, $C\underline{F}_2CF_3$, J = 7.5 Hz); 82.94 (t, 3 F, CF_3, J = 9.5 Hz). MS: found m/z 278.0410 $[M + H]^+$; calculated for $C_9H_7F_7NO$ 278.0409. Found (%): C, 37.41; H, 2.60; N, 4.86. $C_9H_6F_7NO$. Calculated (%): C, 39.00; H, 2.18; N, 5.05.

6-(Furan-2-yl)-4-(heptafluoropropyl)pyridin-2(1*H*)-one (4q) was synthesized by the method *C*, the yield was 592 mg (36%), yellow crystals, m.p. 179—181 °C (acetonitrile). IR, ν/cm^{-1}: 3134 (N—H), 2915—2810 (C—H), 1668 (C=O), 1617 (C=C), 1225—1153 (C—F). ^{1}H NMR, δ: 6.67 (s, 1 H, C(5)H); 6.71—6.72 (m, 1 H, CH_{Fur}); 6.91 (br.s, 1 H, C(3)H); 7.40 (s, 1 H, CH_{Fur}); 7.92 (m, 1 H, CH_{Fur}); 12.29 (br.s, 1 H, NH). ^{13}C NMR, δ: 100.1 (C(5)); 108.1 (tq, $CF_2\underline{C}F_2CF_3$, J = 265.1 Hz, J = 37.8 Hz); 111.6 (C(3)); 112.0 (C(4′)); 112.6 (C(3′)); 114.6 (dt, $\underline{C}F_2CF_2CF_3$, J = 256.6 Hz, J = 31.2 Hz); 118.48 (tt, CF_3, J = 288.2 Hz, J = 33.9 Hz); 139.4 (t, C(4), J = 24.3 Hz); 142.8 (C(5′)); 145.5 (C(2′)); 148.0 (C(6)); 162.6 (C(2)). ^{19}F NMR, δ: 36.40 (s, 2 F, CF_2); 48.82 (br.s, 2 F, CF_2); 83.08 (m, 3 F, CF_3). MS: found m/z 330.0359 $[M + H]^+$; calculated for $C_{12}H_7F_7NO_2$ 330.0360. Found (%): C, 43.71; H, 1.83; N, 4.25. $C_{12}H_6F_7NO_2$. Calculated (%): C, 43.79; H, 1.84; N, 4.26.

Ethyl 4,4,4-trifluoro-3-hydroxy-3-[(6-oxo-4-trifluoromethyl-1,6-dihydropyridin-2-yl)methyl]butanoate (5). A mixture of keto ester **1a** (187 mg, 1 mmol) and 6-methyl-4-(trifluoromethyl)pyridin-2(1*H*)-one **4a** (180 mg, 1 mmol) in 1,4-dioxane (3 mL) was placed in a septum-sealed screw cap vial. Then L-proline (12 mg, 0.1 mmol) was added, and the reaction mixture was magnetically stirred with heating to 80 °C for 3 days. The progress of the reaction was monitored by TLC and ^{19}F NMR spectroscopy. Then the solvent was removed in a rotary evaporator, and the residue was purified by column chromatography (CH_2Cl_2—Et_2O, 8 : 1, as the eluent). The yield was 242 mg (67%), white powder, m.p. 133—135 °C (dichloromethane as the eluent). IR, ν/cm^{-1}: 3409 (N—H, O—H), 3050—2801 (C—H), 1731 (C=O), 1661 (C=O), 1631 (C=C), 1181—1081 (C—F). ^{1}H NMR, δ: 1.19 (t, 3 H, Me, J = 7.0 Hz); 2.68 (dd, 2 H, C(1′)H, J = 25.9 Hz, J = 14.9 Hz); 3.12 (dd, 2 H, C(3′)H, J = 51.6 Hz, J = 13.9 Hz); 4.07 (qd, 2 H, H_2C_{Et}, J = 7.1 Hz, J = 1.5 Hz); 6.47 (br.s, 1 H, C(5)H); 6.64 (s, 2 H, C(3)H, OH); 11.78 (br.s, 1 H, NH). ^{13}C NMR, δ: 13.7 (Me); 35.7 (C(3′)); 38.1 (C(1′)); 60.6 (H_2C_{Et}); 73.45 (q, C(2′), J = 27.4 Hz); 101.2 (C(5)); 115.4 (C(3)); 122.5 (q, CF_3, J = 274.0 Hz); 125.5 (q, CF_3, J = 287.8 Hz); 140.4 (q, C(4), J = 32.8 Hz); 146.0 (C(6)); 161.8 (C(2)); 168.3 (C(4′)). ^{19}F NMR, δ: 83.35 (s, 3 F, CF_3); 97.28 (s, 3 F, CF_3). MS: found m/z 362.0819 $[M + H]^+$; calculated for $C_{13}H_{14}F_6NO_4$ 362.0822. Found (%): C, 43.16; H, 3.69; N, 3.91. $C_{13}H_{13}F_6NO_4$. Calculated (%): C, 43.22; H, 3.63; N, 3.88.

5,6-Dimethyl-4-(trifluoromethyl)pyridin-2(1*H*)-one (6) was synthesized by the method *D*, the yield was 181 mg (19%), and the method *C*, the yield was 86 mg (9%), colorless crystals, m.p. 162—164 °C (acetonitrile). IR, ν/cm^{-1}: 3146 (N—H), 2950, 2833 (C—H), 1665 (C=O), 1616 (C=C), 1170—1032 (C—F). ^{1}H NMR, δ: 2.01, 2.25 (both s, 3 H each, 2 Me); 6.51 (s, 1 H, C(3)H); 12.08 (br.s, 1 H, NH). ^{13}C NMR, δ: 11.9 (Me); 17.2 (Me); 106.3 (C(5)); 114.3 (C(3)); 122.9 (q, CF_3, J = 275.5 Hz); 140.3 (q, C(4), J = 29.5 Hz); 146.7 (C(6)); 160.8 (C(2)). ^{19}F NMR, δ: 99.27 (s, CF_3). MS: found m/z 192.0631 $[M + H]^+$; calculated for $C_8H_9F_3NO$ 192.0631. Found (%): C, 50.19; H, 4.18; N, 7.29. $C_8H_8F_3NO$. Calculated (%): C, 50.27; H, 4.22; N, 7.33.

Evaluation of acute toxicity and analgesic activity. Laboratory animals (Sprague—Dawley rats and CD-1 mice) were obtained from the Nursery for Laboratory Animals "Pushchino" of the Branch of the Shemyakin—Ovchinnikov Institute of Bbioorganic Chemistry of the Russian Academy of Sciences. Second-generation animals were used in the experiments. The animals were kept in polypropylene cages for rats and mice (Bioscape, Germany) with the Zolotoi Kot filler (Zolotoi Pochatok, Voronezh, Russia) under natural dark—light cycle with scheduled access to food (formulation diet for laboratory rats and mice, Delta Feeds, BioPro, Russia) and free access to drinking water. Experiments on laboratory animals were carried out by a professional veterinarian, a pharmacologist, and well-trained technicians in compliance with ethical principles and guidelines for the use of animals in research. The acute toxicity was evaluated in CD-1 albino mice in accordance with standard guidelines.[62] The tested compounds were administered intraperitoneally in a single dose as suspensions in 1% starch mucus, each sample being injected into three animals. The animals were observed for 14 days. The analgesic activity was evaluated using the hot-plate test in Sprague—Dawley rats (3 females and 3 males per group) according to a standard procedure.[63] The compounds were administered intraperitoneally as suspensions in 1% starch mucus. The latency period was determined using a 60200 series Hotplate (TSE Systems, Germany); the measurements were performed 1 and 2 h after the administration of the dose. The maximum time allowed for the animal to stay on the hot plate at 50 °C was set to 30 s to avoid any thermal injury to the paws of the experimental animals. Diclofenac (Hemofarm A.D. Sabac, Serbia) at a dose of 10 mg kg^{-1} was used as the reference compound. The experimental data were processed using the GraphPadPrism 6 software by the Multiple t tests.

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The authors declare no competing interests.

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