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# 5-Trifluoromethoxy-substituted Nicotinic Acid, Nicotinamide and Related Compounds

## Abstract

A practical and convenient method for synthesizing nicotinic acid and nicotinamide with the trifluoromethoxy group in position 5 of the ring has been developed. A series of related compounds, for example, nicotinic aldehyde and nicotinic alcohol, have been synthesized. It has been shown that 3-bromo-5-trifluoromethoxypyridine is a convenient and efficient synthon for palladium-catalyzed coupling reactions. The trifluoromethoxy group has been found to be remarkably stable against hydroiodic acid in contrast to the methoxy group.

***Keywords***: nicotinic acid; nicotinamide; trifluoromethoxy group; antimony trifluoride; fluorination

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**5-Трифлуорометоксизаміщена нікотинова кислота, нікотинамід і споріднені сполуки**

## Анотація

Розроблено практичний і зручний метод синтезу нікотинової кислоти та нікотинаміду з трифлуорометоксигрупою в положенні 5 кільця. Було синтезовано деякі споріднені сполуки, наприклад, нікотиновий альдегід і нікотиновий спирт. З'ясовано, що 3-бромо-5-трифлуорометоксипіридин є зручним синтоном для каталізованих паладієм реакцій сполучення. Визначено, що, на відміну від метоксигрупи, трифлуорометоксигрупа є надзвичайно стійка до дії йодоводневої кислоти.

***Ключові слова***: нікотинова кислота; нікотинамід; трифлуорометоксигрупа; стибій трифлуорид; флуорування

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**Supporting information:** Copies of $^{1}H$, $^{13}C$ and $^{19}F$ NMR spectra of the synthesized compounds.
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## ■ Introduction

A fluorine atom has a privileged position within the halogen family for drugs and agrochemicals design due to its unique properties – small size, high electronegativity, and the ability to form a strong C-F bond. In 2020, about 20% of the commercial pharmaceuticals were fluorine-containing drugs, and their total quantity was 340 compounds. Commonly, they were fluoro-substituted arenes (167 compounds) or heterocycles (20 compounds), as well as trifluoromethylated arenes and heteroarenes (64 compounds). Fluorinated ethers were an important group of pharmaceuticals represented by 18 compounds, among them four were trifluoromethoxylated arenes, namely riluzole (treatment of amyotrophic lateral sclerosis), pretomanid and delamanid (treatment of tuberculosis), and sonidegib (treatment of basal cell carcinoma) [1].


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Nitrogen-containing heterocycles are the most popular compounds for drug design. At least 85% of pharmaceuticals contain such a fragment in their structure. Therefore, it seems unexpected that a small number of drugs with a fluorine-containing heterocyclic ring is known (42 compounds). Moreover, only single fluorine atom or the trifluoromethyl group represent fluorinated substituents [1]. Such circumstances can be explained by the absence of practical and cheap synthetic ways to heterocycles with other fluorinated groups, in particular fluorinated ethers [2]. Methodologies for the synthesis of fluorinated ethers are significantly different from methods for the preparation of alkyl ethers. It is impossible to use trifluoromethyl iodide or trifluoromethyl triflate for direct trifluoromethylation of oxygen nucleophiles in the same way as methyl iodide or methyl triflate. This is due to the strong electronegativity of a fluorine atom that results in reverse polarity of I-$CF_3$ and TfO-$CF_3$ bonds as compared to I-$CH_3$ and TfO-$CH_3$ [2, 3]. A few different strategies can be applied for the preparation of fluorinated ethers. The first method was based on the ether fluorination. It was incorporated into organic chemistry by *Lev Yagupolskii* in 1955 [4]. The main limitation of this method is the harsh conditions of the fluorination stage. Nevertheless, this approach was successfully applied to the synthesis of trifluromethoxy substituted heterocycles [5–7]. Pyridines with the trifluoromethoxy group in various positions of the ring – α-, ß- and γ-substituted pyridines – were obtained by this method. However, this reaction successfully occurred only when at least one α-position of the ring was occupied by a chlorine atom. The same feature was also found to be characteristic for pyrazine derivatives [7]. The second approach to trifluoromethoxylated heterocycles is the cyclization of the fluorinated precursors [8, 9]. A novel route to trifluoromethoxy substituted heterocycles is based on trifluorometylation of the hydroxyl group by the action of hypervalent iodine reagents or direct trifluoromethoxylation [10]. Although the examples of direct trifluoromethoxylation are known from the literature [11], these methods are promising for preparing the α-substituted pyridine ring mainly, at the same time, the synthesis of ß-trifluormethoxipyridine in such a manner is controversial. Direct introduction of the trifluoromethoxy group occurred under more mild reaction conditions than fluorination. Therefore, it can be applied to a wide range of substrates. From the other hand, these methods require expensive reagents that are used in a large excess.

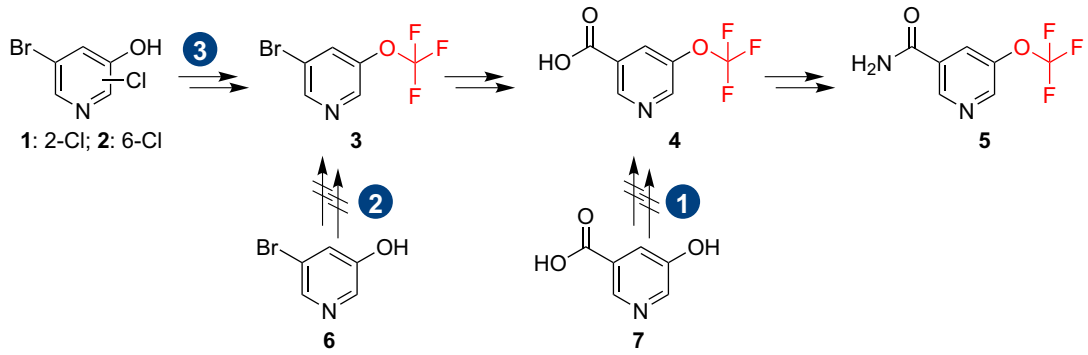
It can be summarized that each of the abovementioned strategies – fluorination of ethers, nucleophilic substitution or direct trifluoromethxylation of hydroxy-compounds – requires some improvements before it becomes a practical method. In the current study, we concentrated our attention on the scalable synthesis of nicotinic acid and related compounds with the trifluoromethoxy group in position 5.

## Results and discussion

A series of trifluoromethoxysubstituted pyridines was prepared earlier [6]. The method used in this paper was based on chlorination-fluorination techniques that allowed to obtain a series of α-chloropyridines with the $OCF_3$-group in various positions. These compounds were used for the preparation of pyridines with different functional groups: amines, aldehydes, acids, silanes, etc. However, 5-trifluoromethoxy substituted nicotinic acid or any suitable precursors for its preparation were not described in this research.

Key compounds for the synthesis of nicotinic acid **4** and nicotinamide **5** with trifluoromethoxy substituent are shown in **Scheme 1**. We found that transformation of 5-hydroxynicotinic acid **7** (or its methyl ester) into the corresponding chlorothionoformate or methylxanthate with further chlorination-fluorination gave no positive results (*route 1*). Similarly, our attempts to transform bromopyridinol **6** to 3-bromo-5-trifluoromethoxypyridine in such a manner failed, despite such transformation was well documented for pyridines with halogen atoms in α-position (*route 2*) [5, 6]. Taking into account this feature of the pyridine ring, α-chloro-substituted pyridines **1** and **2** were used as starting compounds (**Scheme 1**, *route 3*).

We tried to prepare pyridines **10** and **11** according to [6] and found that this procedure was suitable for trichloromethoxysubstituted pyridine **10**, but gave poor results for pyridine **11**. Modifications of the method (reversed mixing of the reagents) allowed us to increase the yield of **11** from 15 to 78% (**Scheme 2**). It should be noted that chlorothionoformates **8** and **9** were used for further transformations without isolation in a pure state. Thus, the methodology proposed is very attractive in terms of handling such toxic compounds. Further fluorination of **10** and **11** by



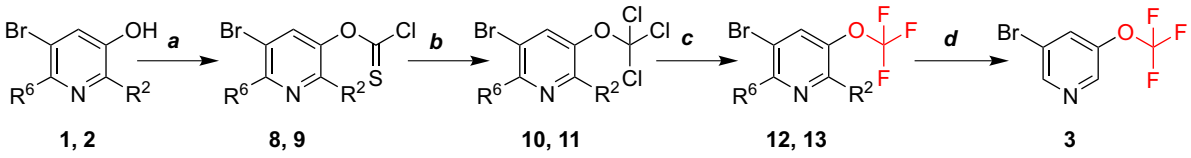
**Scheme 1**. Potential routes to 5-(trifluoromethoxy)nicotinic acid and nicotinamide

antimony trifluoride led to trifluoromethoxysubstituted pyridines **12** and **13**, respectively, in high yields.

For hydrodechlorination reaction of **12** and **13**, we used "red phosphorus / HI" as a reducing agent, and 3-bromo-5-trifluoromethoxypyridine (**3**) was prepared in a high yield. It is noteworthy that the reaction can be performed in a 50 g scale. It is worth mentioning that this reaction required the use of hydroiodic acid as a solvent. However, in contrast to the methoxy group that easily cleaves under these conditions (*Zeisel* determination of ethers [12]), trifluoromethoxy one remains intact even after prolonged heating. No evidence of this group destruction was found in $^{19}$F NMR spectra of the reaction mixture. Thus, both isomers **12** and **13** were successfully transformed into **3** in the same yields. With this in mind, we also used the mixture of chloropyridines **1** and **2** for preparing pyridine **3**. This mixture can be easily obtained by chlorination of 5-bromopyridin-3-ol (**6**) with sodium hypochlorite [13] and, as a result, is more available than individual isomers **1**, **2**.

We have found that 3-bromo-5-trifluoromethoxypyridine (**3**) is a convenient starting material for a wide range of 5-trifluoromethoxysubstituted pyridines (**Scheme 3**). Bromopyridine **3** can be readily lithiated by the action of *n*-buthyllithium, and after the treatment with carbon dioxide, nicotinic acid **4** was formed in almost quantitative yield. This acid was used for preparing 5-trifluoromethoxynicotinamide (**5**) by common methods with a high yield. Lithiated pyridine **3** readily reacted with ethyl formate yielding nicotinic aldehyde **14**. This aldehyde was reduced to alcohol **15** with a high yield.

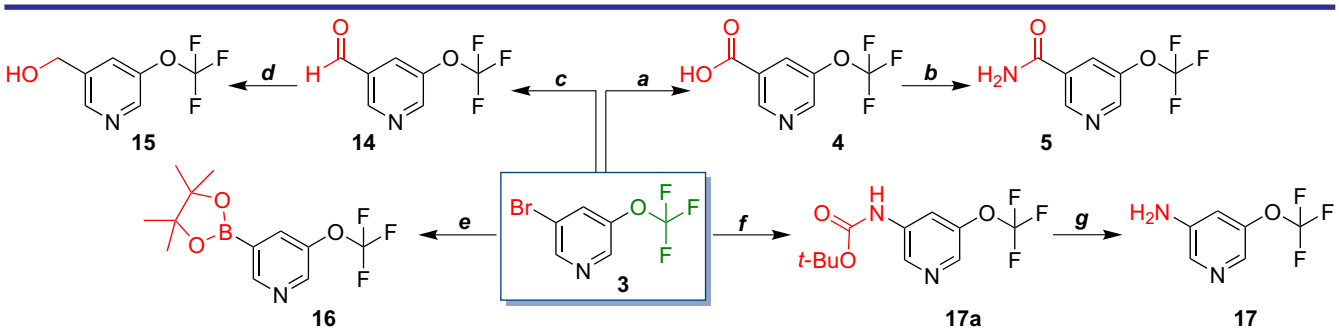
Bromopyridine **3** was also used in palladium-catalyzed cross-coupling reactions. Bromine was substituted with boronic ester under Pd(dppf)Cl$_2$



**1, 8, 10, 12:** $R^2$ = Cl, $R^6$ = H; **2, 9, 11, 13:** $R^2$ = H, $R^6$ = Cl

**Scheme 2**. The synthesis of 3-bromo-5-(trifluoromethoxy)pyridine (**3**)

*Reagents and conditions:* (**a**) $CSCl_2$, NaOH, $CHCl_3/H_2O$, 0 °C; (**b**) $Cl_2$, $CHCl_3$, r.t.; (**c**) $SbF_3$, $SbCl_5$, 145–150 °C; (**d**) P, aq 57 % HI, reflux



**Scheme 3**. The reactivity of 3-bromo-5-(trifluoromethoxy)pyridine

*Reagents and conditions:* (**a**) *n*BuLi, -90 °C, then $CO_2$, 85 % yield; (**b**) $SOCl_2$, 70 °C, then $NH_4OH$, 0 °C, 85 % yield; (**c**) *n*BuLi, -90 °C, then EtOCHO, 64 % yield; (**d**) $NaBH_4$, EtOH, r.t., then aq HCl, r.t., 89 % yield; (**e**) $B_2pin_2$, Pd(dppf)$Cl_2$, KOAc, dioxane, 100 °C, 80 % yield; (**f**) *t*BuOCONH$_2$, $Pd_2dba_3$, Xantphos, $Cs_2CO_3$, dioxane, 100 °C, 69 % yield; (**g**) $CF_3COOH$, $CH_2Cl_2$, r.t., 72 % yield



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catalysis to form pyridine **16**. Compound **3** readily reacted with *tert*-butyl carbamate under $Pd_2dba_3$ catalysis yielding Boc-protected amine **17a**. After deprotection, aminopyridine **17** was obtained in 50% yield in two steps.

Alternatively, we investigated the metalation of chloro-substituted pyridine **13** using *n*-butyllithium (**Scheme 4**). We found that a mixture of nicotinic and isonicotinic acids was formed after treating lithium derivatives with carbon dioxide. If the reaction mixture was saturated by gaseous $CO_2$ at -95–-100°C, a mixture of acids **18**–**19** (1:1) was obtained. When lithiated pyridine was poured onto solid carbon dioxide (-78 °C), the main product was isonicotinic acid **18** (5:1). We supposed that the rearrangement of the initially formed 3-lithium isomer into 4-isomer occurred at temperatures higher than -78 °C due to a strong α-effect of the $OCF_3$ group.

In contrast to nicotinic acids **18** and **19**, nicotinic aldehyde **20** was formed selectively and obtained in a high yield of 79% by the reaction of 3-bromo-2-chloro-5-trifluoromethoxypyridine (**13**) with *n*-butyllithium and further treatment with DMF. In this case isomerization did not occur, probably because the interaction of lithiated pyridine with DMF proceeded faster than with carbon dioxide.

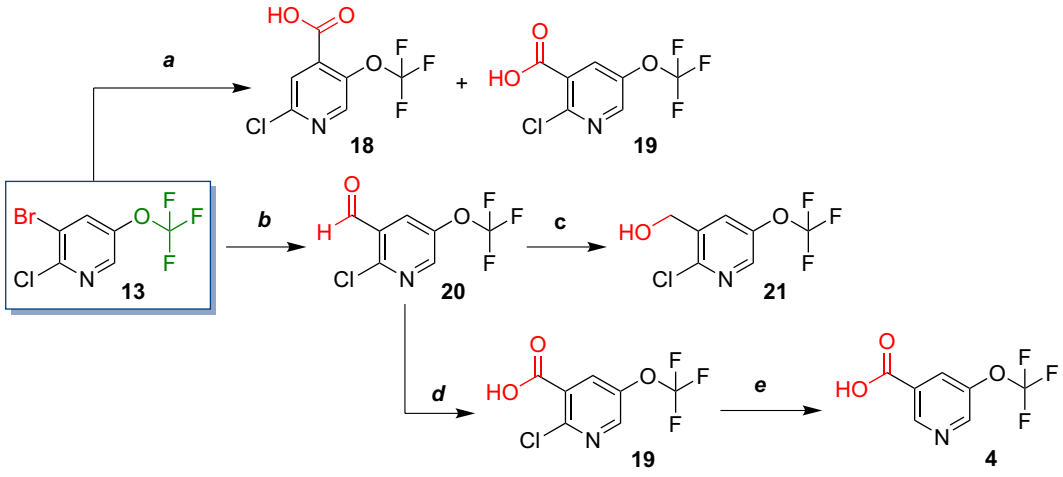
It was shown that this aldehyde **20** could be reduced to alcohol **21** by sodium borohydride or oxidized by potassium permanganate yielding nicotinic acid **19**. In both cases, the target products were obtained in almost quantitative yields. 2-Chloronicotinic acid **19** was used for preparing 5-trifluoromethoxynicotinic acid (**4**). A chlorine atom was reduced by Pd catalysed hydrogenation. This reaction occurred at atmospheric pressure, and the product was obtained in a high yield.

## ■ Conclusion

A synthetic approach based on chlorination-fluorination of the chlorothionoformate group in the pyridine core is a convenient and practical route for trifluoromethoxylated pyridines. The presence of a chlorine atom in α-position of pyridine (either 2 or 6) is necessary for successful transformation, and in both cases 2- or 6-chloro-3-bromo-5-trifluoromethoxysubstituted pyridines are obtained in high yields. In contrast to methoxy group, the trifluoromethoxy one is stable to the hydroiodic acid action. This remarkable property of the trifluoromethoxy group allows to reduce a chlorine atom in α-position of the pyridine ring selectively without destruction of the $OCF_3$ group and reduction of a bromine atom in ß-position of the ring. 3-Bromo-5-trifluoromethoxy pyridine is a promising building block demonstrated by metalation reactions and Pd-catalyzed syntheses. Using this precursor, analogues of natural products– nicotinic acid and nicotinamide with trifluoromethoxy group have been synthesized.

## ■ Experimental part

$^1$H NMR spectra were recorded using a Varian VXR-300 instrument at 300 MHz, a Bruker AVANCE DRX 500 spectrometer at 500 MHz, or a Varian UNITY-Plus 400 instrument at 400 MHz. $^{13}$C NMR spectra (proton decoupled) were recorded on a Bruker AVANCE DRX 500 instrument at 125 MHz, or a Varian UNITY-Plus 400 spectrometer at 100 MHz, or a Varian VXR-300




**Scheme 4**. The synthetic potential of 3-bromo-2-chloro-5-trifluoromethoxypyridine

*Reagents and conditions:* (**a**) *n*BuLi, -90 °C, then $CO_2$; (**b**) *n*BuLi, -90 °C, then DMF, 79% yield; (**c**) $NaBH_4$, EtOH, r.t., then HCl aq, r.t., 94% yield; (**d**) $KMnO_4$, $H_2O$, 60 °C, 80% yield; (**e**) $H_2$, 10% Pd/C, $HCOONH_4$, MeOH, r.t., 79% yield

instrument at 75 MHz. $^{19}F$ NMR spectra were recorded at 376 MHz using a Varian UNITY-Plus 400 spectrometer or at 188 MHz using a Mercury VX 200 Varian instrument. The chemical shifts are given in ppm relative to TMS and $CCl_3F$, respectively, as internal or external standards. The LC-MS spectra were registered on an Agilent 1100 instrument with a diode-matrix and an Agilent 1100 LS/MSD SL mass-selective detector. The GC-MS spectra were registered on a Hewlett-Packard HP GC/MS 5890/5972 instrument (EI 70 eV). The melting points were determined in open capillaries using an SMP3 instrument. The elemental analysis was performed in the Analytical Laboratory of the Institute of Organic Chemistry of mass-selective detector NASU.

For the column chromatography, Merck Kieselgel 60 silica gel was used. Thin-layer chromatography (TLC) was carried out on aluminium-backed plates coated with silica gel (Merck Kieselgel 60 F254).

Unless otherwise stated, commercially available reagents were purchased from Enamine Ltd. (Kyiv, Ukraine) and were used without purification. The solvents were purified according to the standard procedures. Antimony trifluoride was sublimed immediately prior to use. Chlorination of 5-bromopyridin-3-ol with sodium hypochlorite was performed according to [13]. Pure 5-bromo-2-chloro-pyridin-3-ol (M. p. 188 °C) was obtained by $SiO_2$ column chromatography with the mixture of hexane/ethyl acetate (1:4) as an eluent ($R_f$ 0.5).

**Trichloromethoxypyridines (10) and (11). The general procedure**

**Method A.** The solution of thiophosgene (41.4 g, 0.36 mol) in 300 mL of chloroform was added dropwise to the vigorously stirred mixture of hydroxypyridine **1** or **2** (75 g, 0.36 mol) and sodium hydroxide (15.1 g, 0.38 mol) in 300 mL of water at 0 °C, and the mixture was stirred for 2 h at the same temperature. The organic layer was separated, washed with water, and dried over $MgSO_4$. Prepared in such a manner the chloroform solution of chlorothionoformate was saturated with chlorine and stirred for 48 h at room temperature. The excess of chlorine was then removed with $N_2$ gas stream. The solvent was distilled off under reduced pressure (300 mbar), and the residue was distilled in a vacuum yielding the corresponding trichlorometoxypyridine **10** or **11**.

**Method B.** Sodium hydroxide (15.8 g, 0.40 mol) in 300 mL of water was added dropwise to the vigorously stirred mixture of hydroxypyridine **1** or **2** (75 g, 0.36 mol) and thiophosgene (41.4 g, 0.36 mol) in chloroform at 0°C, and the mixture was stirred for 2 h at the same temperature. The organic layer was separated, washed with water, and dried over $MgSO_4$. Prepared in such a manner the chloroform solution of chlorothionoformate was saturated with chlorine and stirred for 48 h at room temperature. The excess of chlorine was removed with $N_2$ gas stream. The solvent was distilled off under reduced pressure (300 mbar), and the residue was distilled in a vacuum yielding the corresponding trichlorometoxypyridine **10** or **11**.

*5-Bromo-2-chloro-3-trichloromethoxypyridine* (**10**)

A colorless oil or a low melted solid. Yield – 64.5 g, 55% (Method A); 72.7 g, 62% (Method B). B. p. 115–117 °C at 0.5 mbar; M. p. 32 °C. Anal. Calcd for $C_6H_2BrCl_4NO$, %: C 22.12, H 0.62, N 4.30. Found, %: C 21.97, H 0.85, N 4.08. $^1H$ NMR (400 MHz, $CDCl_3$), $\delta$, ppm: 8.15 (1H, d, $^3J_{HH}$ = 2.4 Hz, 4-PyH), 8.41 (1H, d, $^3J_{HH}$ = 2.4 Hz, 6-PyH). $^{13}C$ NMR (100 MHz, $CDCl_3$), $\delta$, ppm: 111.5, 117.8, 132.7, 143.7, 144.7, 147.5.

*3-Bromo-2-chloro-5-trichloromethoxypyridine* (**11**)

A colorless oil or a low melted solid. B. p. 120–122 °C at 0.5 mbar; M. p. 45 °C. Yield – 17.7 g, 15% (Method A); 91.5 g, 78% (Method B). Anal. Calcd for $C_6H_2BrCl_4NO$, %: C 22.12, H 0.62, N 4.30. Found, %: C 22.01, H 0.80, N 4.12. $^1H$ NMR (400 MHz, $CDCl_3$), $\delta$, ppm: 8.02 (1H, d, $^3J_{HH}$ = 2.4 Hz, 4-PyH), 8.43 (1H, d, $^3J_{HH}$ = 2.4 Hz, 6-PyH). $^{13}C$ NMR (100 MHz, $CDCl_3$), $\delta$, ppm: 112.1, 119.9, 136.3, 142.2, 147.0, 149.0.

**Trifluoromethoxypyridines (12) and (13). The general procedure**

The corresponding trichloromethoxypyridine **10** or **11** (81.5 g, 0.25 mol) was added in portions to the mixture of $SbF_3$ (134 g, 0.75 mol) and $SbCl_5$ (7.5 g, 0.025 mol) at 100 °C. The mixture was stirred for 5 h at 145–150 °C, cooled to room temperature, mixed with 650 mL of $CH_2Cl_2$, and then quenched with an aqueous solution of $K_2CO_3$ (517 g, 3.75 mol in 2.5 L of water) and KF (653 g, 11.25 mol in 1.25 L of water). The precipitate was filtered off, the organic layer was separated, washed with water, and dried with $MgSO_4$. The solvent was distilled off, and the residue was distilled in a vacuum yielding the corresponding trifluorometoxypyridine **12** or **13**.

*5-Bromo-2-chloro-3-trifluoromethoxypyridine* (**12**)

A colorless oil. Yield – 58.1 g (84%). B. p. 90–92 °C at 20 mbar. Anal. Calcd for $C_6H_2BrClF_3NO$, %: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C 26.07, H 0.73, Cl 12.82. Found, %: C 25.88, H 0.50, Cl 13.04. $^{1}$H NMR (400 MHz, $CDCl_3$), $\delta$, ppm: 7.78 (1H, s, 4-PyH), 8.41 (1H, s, 6-PyH). $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$, ppm: 118.6, 120.3 (q, $^{2}J_{CF}$ = 262.5 Hz, $OCF_3$), 133.1, 142.0, 143.5, 148.4. $^{19}$F NMR (300 MHz, $CDCl_3$), $\delta$, ppm: -57.55 (s, $OCF_3$). GC-MS, *m/z* ($I_{rel}$, %): 277 (100) [M($^{79}$Br$^{37}$Cl)/($^{81}$Br$^{35}$Cl)]$^+$, 275 (79) [M($^{79}$Br$^{35}$Cl)]$^+$, 279 (24) [M($^{81}$Br$^{37}$Cl)]$^+$.

*3-Bromo-2-chloro-5-trifluoromethoxypyridine* (**13**)

A colorless oil. Yield – 63.1 g (91%). B. p. – 105–107 °C at 20 mbar. Anal. Calcd for $C_6H_2BrClF_3NO$, %: C 26.07, H 0.73, Cl 12.82. Found, %: C 25.80, H 0.55, Cl 12.49. $^{1}$H NMR (300 MHz, $CDCl_3$), $\delta$, ppm: 7.86 (1H, dd, $^{3}J_{HH}$ = 2.4 Hz, $^{4}J_{HF}$ = 1.8 Hz, 4-PyH), 8.32 (1H, dd, $^{3}J_{HH}$ = 2.4 Hz, $^{4}J_{HF}$ = 1.8 Hz, 6-PyH). $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$, ppm: 120.2 (q, $^{1}J_{CF}$ = 260.5 Hz, $OCF_3$), 120.3, 134.6, 140.7, 144.4, 148.9. $^{19}$F NMR (300 MHz, $CDCl_3$), $\delta$, ppm: -58.93 (s, $OCF_3$). GC-MS, *m/z* ($I_{rel}$, %): 277 (100) [M($^{79}$Br$^{37}$Cl)/($^{81}$Br$^{35}$Cl)]$^+$, 275 (79) [M($^{79}$Br$^{35}$Cl)]$^+$, 279 (24) [M($^{81}$Br$^{37}$Cl)]$^+$.

**The synthesis of 3-bromo-5-trifluoromethoxypyridine (3)**

The mixture of 3-bromo-2-chloro-5-trifluoromethoxypyridine (**13**) (63.0 g, 0.23 mol) and red phosphorus (85.0 g, 2.75 mol) in 1 L of 57% aqueous HI was refluxed for 48 h. The progress of the reaction was monitored by $^{19}$F NMR spectra. The excess of phosphorus was filtered off *via* a glass filter, and the resulting solution was poured into the solution of $Na_2CO_3$ (400 g, 3.8 mol) in 2.5 L of water. The product was extracted with $CH_2Cl_2$ (6×400 mL), the extract obtained was washed with water (3×250 mL), and dried with $MgSO_4$. The solvent was distilled off, and the residue was distilled in a vacuum yielding pyridine **3** (50.2 g, 90%).

5-Bromo-2-chloro-3-trifluoromethoxypyridine (**12**) (63 g, 0.23 mol) was used for preparing pyridine **3** (46.2 g, 83%) by the same procedure. When the mixture of chlorinated pyridines **12** and **13** in the ratio of 4:1 (50 g, 0.18 mol) was used for this reaction, bromopyridine **3** was obtained in 83% yield (36.3 g).

A colorless oil. B. p. 100–105 °C at 70 mbar. Anal. Calcd for $C_6H_3BrF_3NO$, %: C 29.78, H 1.25, Br 33.02. Found, %: C 29.88, H 1.53, Br 32.85. $^{1}$H NMR (400 MHz, $CDCl_3$), $\delta$, ppm: 7.73 (1H, s, 4-PyH), 8.48 (1H, s, 2/6-PyH), 8.63 (1H, s, 2/6-PyH). $^{13}$C NMR (75 MHz, $CDCl_3$), $\delta$, ppm: 120.3 (q, $^{1}J_{CF}$ = 260.7 Hz, $OCF_3$), 120.4, 131.4, 141.1, 145.9, 149.4. $^{19}$F NMR (300 MHz, $CDCl_3$), $\delta$, ppm: -58.74 (s, $OCF_3$). GC-MS, *m/z* ($I_{rel}$, %): 241 (100) [M($^{79}$Br)]$^+$, 243 (98) [M($^{81}$Br)]$^+$.

**The preparation of 5-trifluoromethoxynicotinic acid (4) from bromopyridine (3)**

*n*-Butyllithium (2.5 M solution in hexane, 7 mL, 17.4 mmol) was added to 25 mL of vigorously stirred toluene at -70– -65 °C. After the addition was completed, bromopyridine **3** (4 g, 16.5 mmol) was added at the same temperature, and the mixture was stirred for additional 30 min. Then the mixture was cooled to -85–-90 °C, and 12 mL of THF were added. The reaction mixture was stirred for 15 min, then poured into crushed dry ice (*ca.* 15 g). The product was extracted with aqueous sodium hydroxide solution (2 g, 50 mmol in 40 mL of water), washed with MTBE, and acidified with 3% aqueous hydrochloric acid to pH 5.5. The precipitate was filtered and crystallized (water/ethanol 5-to-1 mixture) yielding nicotinic acid **4** (2.9 g, 85%).

**The preparation of 5-trifluoromethoxynicotinic acid (4) from 2-chloro-5-(trifluoromethoxy)nicotinic acid (19)**

The mixture of 2-chloronicotinic acid **19** (0.5 g, 2 mmol), ammonium formate (0.2 g, 3 mmol) and 10% Pd on charcoal (0.2 g) in methanol (10 mL) was stirred in hydrogen atmosphere for 24 h. The mixture was filtered, the solvent was evaporated in a vacuum, and the residue was diluted with 3% hydrochloric acid and extracted with ethyl acetate. The organic solution was dried with $MgSO_4$, evaporated in a vacuum yielding nicotinic acid **4** (0.33 g, 79%).

*5-Trifluoromethoxynicotinic acid* (**4**)

A colorless powder. M. p. 148–149 °C. Anal. Calcd for $C_7H_4F_3NO_3$, %: C 40.60, H 1.95. Found, %: C 40.48, H 2.13. $^{1}$H NMR (500 MHz, DMSO-$d_6$), $\delta$, ppm: 8.19 (1H, s, 4-PyH), 8.90 (1H, s, 2/6-PyH), 9.08 (1H, s, 2/6-PyH). $^{13}$C NMR (125 MHz, DMSO-$d_6$), $\delta$, ppm: 120.4 (q, $^{1}J_{CF}$ = 257.7 Hz, $OCF_3$), 128.6, 129.4, 145.5, 146.8, 149.4, 165.3. $^{19}$F NMR (470 MHz, DMSO-$d_6$), $\delta$, ppm: -58.38 (s, $OCF_3$). LC-MS, *m/z* (CI): 207 [M]$^+$.

**The synthesis of 5-(trifluoromethoxy)nicotinamide (5)**

Nicotinic acid **4** (1 g, 4.8 mmol) was added in portions to thionyl chloride (2.9 g, 24 mmol) at 0 °C. The mixture was stirred at 70 °C for 2 h until the evolution of gas was completed. The excess of thionyl chloride was distilled off in a vacuum, and the residue was dissolved in MTBE (10 mL). A concentrated aqueous solution of ammonia (2 mL) was added dropwise to the solution at 0 °C, and the precipitate formed was filtered and dried in a vacuum.

A colorless powder. Yield – 0.85 g (85%). M. p. 147–148 °C. Anal. Calcd for $C_7H_5F_3N_2O_2$, %: C 40.79, H 2.45, N 13.59. Found, %: C 40.60, H 2.55, N 13.70. $^1$H NMR (400 MHz, DMSO-$d_6$), $\delta$, ppm: 7.82 (1H, s, $NH_2$), 8.22 (1H, s, 4-PyH), 8.32 (1H, s, $NH_2$), 8.83 (1H, s, 2/6-PyH), 9.07 (1H, s, 2/6-PyH). $^{13}$C NMR (125 MHz, DMSO-$d_6$), $\delta$, ppm: 120.4 (q, $^1J_{CF}$ = 257.7 Hz, $OCF_3$), 128.6, 129.4, 145.5, 146.8, 149.4, 165.3. $^{19}$F NMR (376 MHz, DMSO-$d_6$), $\delta$, ppm: -57.68 (s, $OCF_3$). LC-MS, *m/z* (CI): 207 $[M+H]^+$.

**The procedure for 5-trifluoromethoxynicotinaldehyde (14)**

*n*-Butyllithium (2.5 M solution in hexane, 7 mL, 17.4 mmol) was added to 25 mL of vigorously stirred toluene at -70–-65 °C. After the addition was completed, the solution of bromopyridine **3** (4 g, 16.5 mmol) in toluene (10 mL) was added to the mixture at the same temperature, and the mixture was stirred for further 30 min. The reaction mixture was cooled to -85–-90 °C, 12 mL of THF was added, the reaction mixture was stirred for 15 min, ethyl formate (1.5 g, 20 mmol) was added dropwise at the same temperature. After the addition was completed, the mixture was warmed to -10 °C, and the solution of $NaHSO_4$ (4 g, 33 mmol) in 10 mL of water was added. The product was extracted with MTBE, the extract obtained was washed with a brine, and dried with $MgSO_4$. The solvent was distilled off, and the residue was distilled in a vacuum yielding nicotinic aldehyde **14** as a colorless oil.

Yield – 2 g (64%). B. p. 50–52 °C at 0.5 mbar. Anal. Calcd for $C_7H_4F_3NO_2$, %: C 43.99, H 2.11, N 7.33. Found, %: C 42.71, H 2.35, N 7.12. $^1$H NMR (300 MHz, $CDCl_3$), $\delta$, ppm: 8.01 (1H, s, 4-PyH), 8.77 (1H, s, 6-PyH), 9.02 (1H, s, 2-PyH), 10.15 (1H, s, CHO). $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$, ppm: 120.3 (q, $^2J_{CF}$ = 260.5 Hz, $OCF_3$), 126.7, 132.3, 146.5, 147.9, 149.9, 189.0. $^{19}$F NMR (188 MHz, $CDCl_3$), $\delta$, ppm: -58.38 (s, $OCF_3$). GC-MS, *m/z* ($I_{rel}$, %): 191 (100) $[M]^+$.

**The preparation of 5-trifluoromethoxypyridin-3-yl-methanol (15)**

Sodium borohydride (0.6 g, 15 mmol) was added to the solution of 5-(trifluoromethoxy)nicotinaldehyde (**14**) (1 g, 5 mmol) in ethanol (30 mL) at 0 °C, and the mixture was stirred at room temperature for 4 h. The solvent was evaporated in vacuum, and 10 mL of water was added to the mixture. The mixture was acidified with 10% aqueous HCl to pH 1–2, stirred at room temperature for 12 h, and then neutralized with $NaHCO_3$. The product was extracted with MTBE, the extract was dried over $MgSO_4$. The solvent was distilled off, and the residue was distilled in a vacuum to give alcohol **15** as a colorless oil.

Yield – 0.85 g (89%). B. p. 92–93 °C at 0.5 mbar. Anal. Calcd for $C_7H_6F_3NO_2$, %: C 43.53, H 3.13, N 7.25. Found, %: C 43.37, H 3.33, N 7.22. $^1$H NMR (300 MHz, $CDCl_3$), $\delta$, ppm: 4.06 (1H, br. s, OH), 4.73 (2H, s, C$\underline{H_2}$OH), 7.60 (1H, s, 4-PyH), 8.33 (1H, s, 2/6-PyH), 8.40 (1H, s, 2/6-PyH). $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$, ppm: 61.3 ($\underline{C}H_2OH$), 120.3 (q, $^1J_{CF}$ = 260.0 Hz, $OCF_3$), 127.0, 138.6, 141.3, 146.0, 146.3. $^{19}$F NMR (188 MHz, $CDCl_3$), $\delta$, ppm: -58.66 (s, $OCF_3$). GC-MS, *m/z* ($I_{rel}$, %): 193 (100) $[M]^+$.

**The preparation of 3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-5-trifluoromethoxypyridine (16)**

The mixture of bromopyridine **3** (6 g, 25 mmol), bis(pinacolato)diboron (8.2 g, 32 mmol), potassium acetate (9.7 g, 100 mmol) and Pd(dppf)$Cl_2$·$CH_2Cl_2$ (1 g, 1.2 mmol) in 90 mL of dioxane was stirred for 24 h at 95–100 °C under argon atmosphere. The mixture was cooled to room temperature, filtered through a $SiO_2$ pad, diluted with water (150 mL), and extracted with MTBE. The product was purified by $SiO_2$ column chromatography using a mixture of hexane/MTBE in 3:1 as an eluent ($R_f$ 0.3).

A colorless powder. Yield – 5.8 g (80%). M. p. 35–37 °C. Anal. Calcd for $C_{12}H_{15}BF_3NO_3$, %: C 49.86, H 5.23. Found, %: C 50.01, H 5.40. $^1$H NMR (300 MHz, $CDCl_3$), $\delta$, ppm: 1.35 (12H, s, 4×$CH_3$), 7.90 (1H, s, 4-PyH), 8.59 (1H, s, 2/6-PyH), 8.86 (1H, s, 2/6-PyH). $^{13}$C NMR (150 MHz, $CDCl_3$), $\delta$, ppm: 24.6 ($CH_3$), 84.6 ($\underline{C}(CH_3)_2$), 118.3, 120.3 (q, $^1J_{CF}$ = 260.1 Hz, $OCF_3$), 133.9, 145.0, 145.8, 153.4. $^{19}$F NMR (300 MHz, $CDCl_3$), $\delta$, ppm: -58.0 (s, $OCF_3$). GC-MS, *m/z* ($I_{rel}$, %): 289 (100) $[M(^{11}B)]^+$, 288 (26) $[M(^{10}B)]^+$.

***tert*-Butyl 5-(trifluoromethoxy)pyridin-3-yl-carbamate (17a)**

The mixture of bromopyridine **3** (4.8 g, 20 mmol), *tert*-butyl carbamate (3.5 g, 30 mmol), caesium carbonate (13 g, 40 mmol), $Pd_2dba_3$ (0.9 g, 1 mmol) and Xantphos (0.6 g, 1 mmol) in 50 mL of dioxane were stirred for 24 h at 95–100 °C under argon atmosphere. The mixture was cooled to room temperature, filtered through a $SiO_2$ pad, diluted with water (150 mL), and extracted with MTBE. The product was purified by $SiO_2$ column chromatography using the mixture of hexane/ethyl acetate (5:1) as an eluent ($R_f$ 0.2).

A colorless powder. Yield – 3.8 g (69%). M. p. 60–62 °C. Anal. Calcd for $C_{11}H_{13}F_3N_2O_3$, %: C 47.49,


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H 4.71, N 10.07. Found, %: C 47.28, H 4.88, N 10.24. $^1$H NMR (400 MHz, $CDCl_3$), $\delta$, ppm: 1.55 (9H, s, *t*-Bu), 7.38 (1H, s, 4-PyH), 8.22 (1H, s, 2/6-PyH), 8.48 (1H, s, NH). $^{13}$C NMR (125 MHz, $CDCl_3$), $\delta$, ppm: 28.2 (C($\underline{C}H_3$)$_3$), 81.8 ($\underline{C}$(CH$_3$)$_3$), 118.3, 120.4 (q, $^1J_{CF}$ = 260.2 Hz, $OCF_3$), 135.9, 137.2, 137.5, 146.4, 152.7. $^{19}$F NMR (300 MHz, $CDCl_3$), $\delta$, ppm: -58.54 (s, $OCF_3$).

**3-Amino-5-trifluoromethoxypyridin (17)**

The mixture of compound ***Boc*-17** (3.8 g, 14 mmol) and trifluoroacetic acid in $CH_2Cl_2$ were stirred at room temperature for 20 h. The mixture was neutralized with sodium carbonate, washed with water, and dried with $MgSO_4$. The solvent was distilled off, and the residue was distilled in a vacuum to yield pyridine **17** as a colorless solid.

Yield – 1.8 g (72%). B. p. 60–62 °C at 1 mbar; M. p. 35–37 °C. Anal. Calcd for $C_6H_5F_3N_2O$, %: C 40.46, H 2.83, N 15.73. Found, %: C 40.31, H 3.01, N 15.55. $^1$H NMR (400 MHz, $CDCl_3$), $\delta$, ppm: 4.09 (2H, s, NH), 6.87 (1H, s, 4-PyH), 7.95 (1H, s, 2/6-PyH), 8.06 (1H, s, 2/6-PyH). $^{13}$C NMR (125 MHz, $CDCl_3$), $\delta$, ppm: 118.0, 120.5 (q, $^1J_{CF}$ = 260.0 Hz, $OCF_3$), 136.0, 137.0, 137.5, 146.6, 152.7. $^{19}$F NMR (300 MHz, $CDCl_3$), $\delta$, ppm: -58.5 (s, $OCF_3$). GC-MS, *m*/*z* ($I_{rel}$, %): 178 (100) $[M]^+$.

**2-Chloro-5-trifluoromethoxy-nicotinaldehyde (20)**

*n*-Butyllithium (2.5 M solution in hexane, 4.6 mL, 11.5 mmol) was added to 20 mL of vigorously stirred toluene at -70–-65 °C. After the addition was complete, the solution of pyridine **13** (3 g, 10.8 mmol) in toluene (10 mL) was added to the mixture at the same temperature, and the mixture was stirred for further 30 min. The reaction mixture was cooled to -90–-85 °C, and 10 mL of THF was added, the reaction mixture was stirred for 15 min, then DMF (2.4 g, 30 mmol) was added dropwise at the same temperature. After the addition was completed, the mixture was warmed to -10 °C, and the solution of $NaHSO_4$ (2.9 g, 20 mmol) in 10 mL of water was added. The product was extracted with MTBE, the extract was washed with a brine, dried over $MgSO_4$. The solvent was distilled off, and the residue was distilled in a vacuum to give chloronicotinic aldehyde **20** as a colorless oil.

Yield – 1.9 g (79%). B. p. 65–66 °C at 1 mbar. Anal. Calcd for $C_7H_3ClF_3NO_2$, %: C 37.28, H 1.34, N 6.21. Found, %: C 37.30, H 1.55, N 6.12. $^1$H NMR (500 MHz, $CDCl_3$), $\delta$, ppm: 8.05 (1H, s, 4-PyH), 8.51 (1H, s, 6-PyH), 10.37 (1H, s, CHO). $^{13}$C NMR (125 MHz, $CDCl_3$), $\delta$, ppm: 120.1 (q, $^1J_{CF}$ = 261.5 Hz, $OCF_3$), 129.2, 129.5, 145.6, 146.9, 150.6, 178.8. $^{19}$F NMR (188 MHz, $CDCl_3$), $\delta$, ppm: -57.92 (s, $OCF_3$). GC-MS, *m*/*z* ($I_{rel}$, %): 225 (100) $[M(^{35}Cl)]^+$, 227 (30) $[M(^{35}Cl)]^+$.

**2-Chloro-5-(trifluoromethoxy)pyridin-3-yl-methanol (21)**

Sodium borohydride (0.95 g, 25 mmol) was added to the solution of 2-chloro-5-(trifluoromethoxy)nicotinaldehyde (**20**) (1.9 g, 8.4 mmol) in ethanol (40 mL) at 0 °C, and the mixture was stirred at room temperature for 4 h. The solvent was evaporated in a vacuum, and 10 mL of water was added to the mixture. The mixture was acidified with 10% aqueous HCl to pH 1–2, stirred at room temperature for 12 h, and then neutralized with $NaHCO_3$. The product was extracted with MTBE, the extract was dried with $MgSO_4$. The solvent was distilled off, and the residue was distilled in a vacuum to give alcohol **23** as a colorless oil.

Yield – 1.8 g (94%). B. p. 101–102 °C at 0.5 mbar. Anal. Calcd for $C_7H_5F_3NO_2$, %: C 36.95, H 2.21, Cl 15.58. Found, %: C 36.90, H 2.28, Cl 15.55. $^1$H NMR (400 MHz, $CDCl_3$), $\delta$, ppm: 2.25 (1H, br. s, OH), 4.78 (2H, s, C$\underline{H_2}$OH), 7.83 (1H, s, 4-PyH), 8.22 (1H, s, 6-PyH). $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta$, ppm: 61.2 ($\underline{C}H_2OH$), 120.3 (q, $^1J_{CF}$ = 260.0 Hz, $OCF_3$), 127.0, 138.6, 141.3, 146.0, 146.3. $^{19}$F NMR (188 MHz, $CDCl_3$), $\delta$, ppm: -58.84 (s, $OCF_3$). GC-MS, *m*/*z* ($I_{rel}$, %): 227 (100) $[M(^{35}Cl)]^+$, 225 (30) $[M(^{35}Cl)]^+$.

**2-Chloro-5-(trifluoromethoxy)nicotinic acid (19)**

Potassium permanganate (0.46 g, 3 mmol) was added to a mixture of aldehyde **20** (1 g, 4.4 mmol) and potassium carbonate (0.11 g, 0.8 mmol) in water (10 mL) at 50–60 °C. The mixture was stirred for 1 h at 60 °C, cooled to room temperature, filtered, and the water solution was acidified to pH 6 with 3% aqueous hydrochloric acid. The product was filtered off, washed with water, and dried in a vacuum.

A colorless powder. Yield – 0.85 g (80%). M. p. 142–143 °C. Anal. Calcd for $C_7H_3ClF_3NO_3$, %: C 34.81, H 1.25, Cl 14.68. Found, %: C 34.50, H 1.55, Cl 14.82. $^1$H NMR (300 MHz, DMSO-$d_6$), $\delta$, ppm: 8.24 (1H, s, 4-PyH), 8.89 (1H, s, 6-PyH), 13.76 (1H, br. s, COOH). $^{13}$C NMR (75 MHz, DMSO-$d_6$), $\delta$, ppm: 116.4 (q, $^1J_{CF}$ = 260.5 Hz, $OCF_3$), 125.2, 128.1, 131.7, 147.0, 148.8, 164.2. $^{19}$F NMR (188 MHz, DMSO-$d_6$), $\delta$, ppm: -57.34 (s, $OCF_3$). LC-MS, *m*/*z* (CI): 241 $[M(^{35}Cl)+H]^+$, 243 $[M(^{35}Cl)+H]^+$.

**The metalation of 3-bromo-2-chloro-5-trifluoromethoxy-pyridine (13) using *n*-butyllithium with the formation of the mixture of isonicotinic (18) and nicotinic acids (19)**

*n*-Butyllithium (2.5 M solution in hexane, 4.6 mL, 11.5 mmol) was added to 20 mL of vigorously stirred toluene at -70–-65 °C. After the addition was completed, the solution of pyridine **13** (3 g, 10.8 mmol) in toluene (10 mL) was added to the mixture at the same temperature, and the resulting mixture was stirred for further 30 min. The reaction mixture was cooled to -90–-85 °C, and 10 mL of THF was added, the reaction mixture was stirred for 15 min, then gaseous $CO_2$ (4.8 g, 0.11 mol) was bubbled through the reaction mixture at -90–-85 °C. After the addition was completed, the mixture was warmed to room temperature, washed with MTBE, acidified with 5% hydrochloric acid to pH 2. The products were filtered off, washed with water, and dried in a vacuum.

The yield of the mixture of isonicotinic **18** and nicotinic **19** acids (1:1) was 1.95 g (75%). In the case when the reaction mixture after the addition of THF and stirring for 15 min at -90–-85 °C was poured into crushed dry ice, the yield of the mixture of acids **18** and **19** (5:1) was 2.2 g (84%). The structures of products were determined by $^{1}H$ and $^{19}F$ NMR and LC-MS methods. They were in good agreement with [6] for 2-chloro-5-(trifluoromethoxy)isonicotinic acid (**18**), and the sample of pure 2-chloro-5-(trifluoromethoxy)nicotinic acid (**19**) prepared by oxidation of aldehyde **20**.

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