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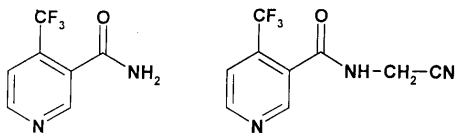
A SIMPLE AND CONVENIENT APPROACH TO BIOLOGICALLY ACTIVE 4-TRIFLUOROMETHYLNICOTINIC ACID DERIVATIVES

A simple and convenient synthesis of biologically active 4-trifluoromethylnicotinic acid derivatives such as amide, esters and nitril has been developed.

INTRODUCTION. Insecticides are the second largest market segment for crop protection chemicals with total global sales of more then 6.5 billion €/pa in 2004. The search for new insecticides which have an improved efficacy, low mammalian toxicity, more favourable environmental profile and lower cost is a truly challenging task for R&D chemists within the crop protection companies dealing with development and manufacturing of new pest control products.

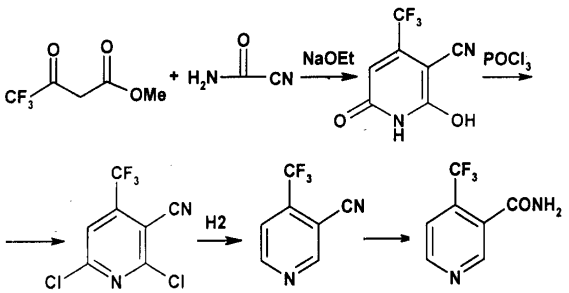
Fluorine as a substituent in active ingredients plays a significant and increasingly important role. Currently, about 15 % of the pesticides listed in the 13th edition of the Pesticide Manual contain at least one fluorine atom [1]. The biggest group of fluorinated pesticides are the compounds containing a trifluoromethyl group (mainly in aromatic rings), followed by aromatic compounds containing an isolated fluorine atom (one and more). It was estimated that the number of fluorinated compounds currently under development represent some 35—50 % of the all active ingredients under development.

4-Trifluoromethylpyridine carboxamides are an excellent example of the positive impact of fluorine on the biological profile of an active ingredient. The insecticidal activity of 4-trifluoromethylnicotinic acid amide was first published in 1994 [2]. Since that time, a large number of patent applications have subsequently been published claiming the pesticidal potential of this class of compounds [3—13]. These 4-trifluoromethylnicotinic acid amides belong to a new generation of modern systemic and contact insecticides. They are active against sucking pests such as aphids and white flies and have a novel mode of action which is different from all currently known products. The first product of this class Flonicamid® has already entered the market:

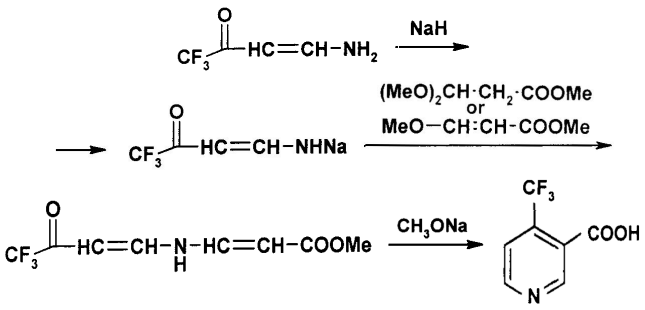


4-Trifluoromethylnicotinamide Flonicamid®

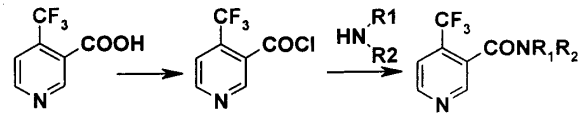
EXPERIMENTAL RESULTS AND DISCUSSION. The first synthetic pathway to 4-trifluoromethylnicotinic amide, with trifluoromethyl-2-pyridone [14] (prepared via cyclisation of 4,4,4-trifluoroacetoacetate) as the key intermediate, was published in 1994 [2, 6].



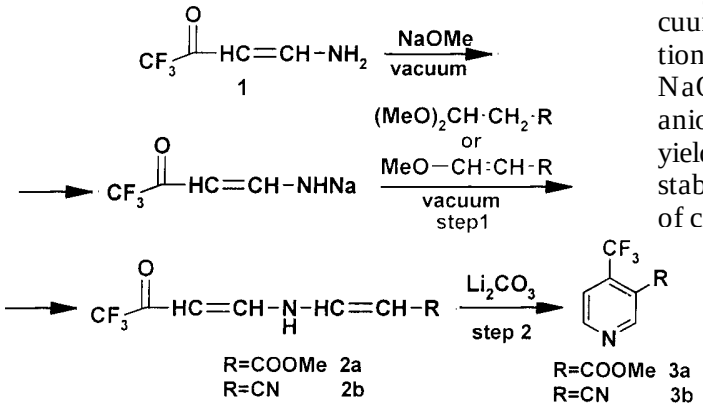
A more practical and efficient way for the preparation of 4-trifluoromethylnicotinic acid, starting from the more easily available 4-amino-1,1,1-trifluoro-3-buten-2-on [15], was reported in 1996 [16]:



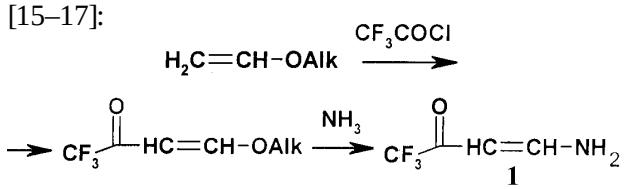
During the cyclisation with sodium methanolate, saponification of the carbomethoxy group also occurred, so that the acid rather the ester was the product of this reaction. For the synthesis of the desired nicotinamides, the nicotinic acid had to be additionally activated, usually via reaction with thionyl chloride:



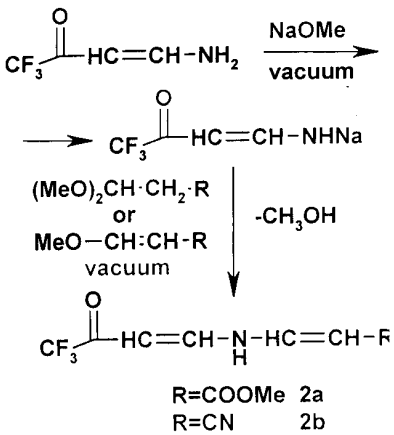
Recently, we developed a simple and convenient two step procedure for the preparation of 4-trifluoromethylnicotinic acid derivatives, such as nitriles and esters, starting from commercially available 4-amino-,1,1,1-trifluoro-3-buten-2-one:



The starting material in the new synthesis 4-amino-1,1,1-trifluoro-3-buten-2-one (1) can be easily prepared according to the literature procedure, whereby both trifluoroacetic acid anhydride and the cheaper trifluoroacetic acid chloride can be used for the *Hojo* acylation of alkylvinyl ethers to give 4-alkoxy-1,1,1-trifluoro-3-buten-3-one. Subsequent reaction with gaseous ammonia proceeds exothermically to give 4-amino-1,1,1-trifluoro-3-buten-2-one in a high yield [15–17]:



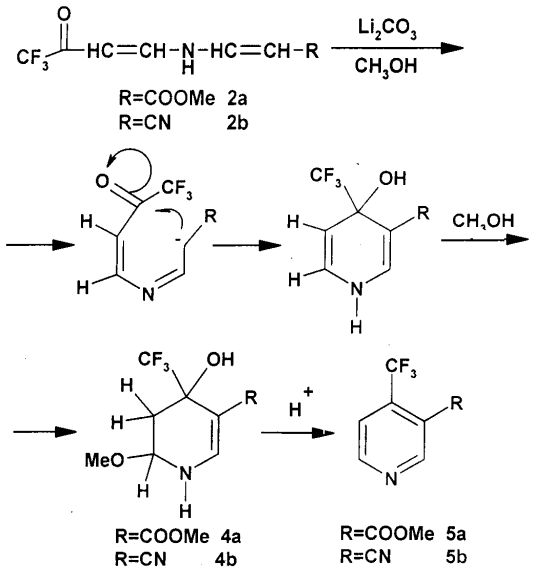
4-Amino-1,1,1-trifluoro-3-buten-2-one (1), b.p. 54 °C/0.4 mbar [15], is thermally and hydrolytically labile. The thermal instability (decomposition onset: 70 °C) makes batch distillation virtually impossible (on any reasonable scale) for safety reasons. TFD (thin film distillation) could be successfully used to give a product of 95—98 % purity. The next step in the synthesis is the base-catalysed condensation of this vinylamino ketone with activated acrylic acid derivatives to form the desired bis(vinyl)amine (2a,b). We have now found that KOtBu, NaOtBu or even NaOMe in DMF or NMP can be successfully used for the generation of the highly reactive anion from vinylaminoketone instead of the more hazardous sodium hydride which was originally used for the activation [2]. 4-Amino-1,1,1-trifluoro-3-buten-2-one (1) shows only moderate stability in methanol or other alcohols. The decomposition is accelerated by the presence of strong bases e.g.: alcoholates leading to the formation of tarry polymeric products. The removal (under vacuum) of the methanol formed during the generation of the anion from the vinylaminoketone and NaOMe, or during the reaction of the generated anion with acrylic acids derivatives, improves the yield of this transformation significantly. The solid, stable bis(vinyl)amine (2a,b) is formed as a mixture of cis/trans isomers:



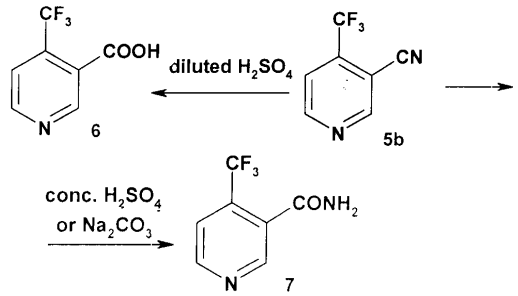
Upon heating the bisvinylamines (2a), with a catalytic amount of Li_2CO_3 or K_2CO_3 (1–10 % mol.) in methanol, the ring closure proceeds smoothly yielding a diastereomeric mixture of two dihydropyridines (4a,b). These diastereoisomers, in the case that R=COOMe, can be separated and isolated in pure form using column chromatography.

The exact structure of these compounds using X-ray analysis is not yet defined. Acidification of the reaction mixture gives the desired 4-trifluoromethyl-3-cyano- or 4-trifluoromethyl-3-carbomethoxy-

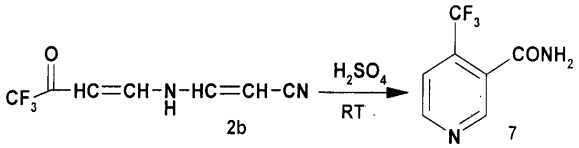
pyridine (5a,b) in a high yield:



The nitrile (5b) can be easily transformed into the acid (6) or the amide (7) by heating with H_2SO_4 or by heating with an aqueous solution of Na_2CO_3:

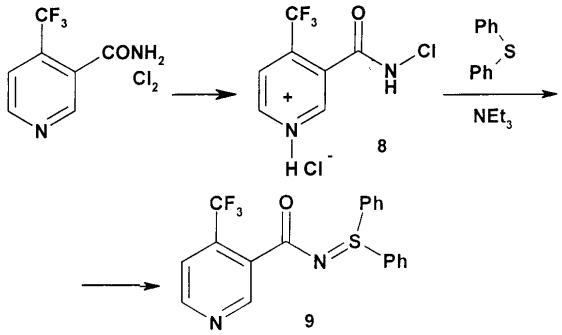


Surprisingly, we found that the bisvinylamine (2b) undergoes internal cyclisation producing 4-trifluormethylnicotine amide (5) as a single product upon being dissolved in concentrated H_2SO_4. The complete transformation proceeds in concentrated sulphuric acid at room temperature within 6–10 h to give 4-trifluoromethylnicotine amide (7) in 80–85



Until now, we were not able to clarify the mechanism of this reaction, but we assume that the hydrolysis of the nitrile group proceeds simultaneously or before the cyclisation step takes place. Supporting this proposal, is the fact that the hydrolysis of the nitrile group in 4-trifluoromethyl-3-cyanopyridine requires heating of the compound at 120—140 °C with concentrated H_2SO_4 for 4 h. 4-Trifluoromethylnicotinic acid amide (7) itself shows strong insecticidal activity [2]. Further derivatisation of the amide enhances the insecticide action of the molecule and improves the spectrum of insecticidal activity [3–13].

For the preparation of 4-trifluoromethylnicotinic acid amides the corresponding acid, acid chloride, ester or primary amide are used. A large group of biologically active compounds containing a sulfimino group are prepared from the N-chloronicotinamide which was primarily obtained via chlorination of the nicotinamide with tert-butylhypochlorite [18]. In more recent experiments it has been found that this dangerous process can be replaced by chlorination with Cl_2 in diluted (5 %) HCl solution [14, 20]. N-Chloro-4-trifluoronicotin-amide is obtained and isolated from aqueous solution as a stable and non-hygroscopic hydrochloric salt. This then treated with different dialkyl- and diarylsulfides [18] to give the corresponding biologically active sulphur imines, for instance containing diphenylsulphide moiety.:



These sulfimines show very high systemic insecticidal activity against sucking pests causing cessation of feeding after approx 30 min, and death of the aphids within 2–3 days after application [18]. In summary we have described the newly developed synthesis of trifluoromethylnicotinic acid derivatives which is significantly easier and cheaper than the previously known synthesis options. Furthermore, this novel synthetic pathway to the new generation of highly potent systemic and contact insecticides enables considerable derivatisation at various positions of the molecules.

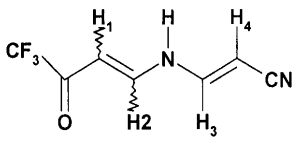
Commercially available chemicals were of analytical grade and used without purification. ^{1}H and ^{19}F NMR spectra were measured on a Bruker Avance 400 NMR Spectrometer (400.13 MHz, for ^{1}H NMR and 376.47 MHz, for ^{19}F NMR) with TMS and $CFCl_3$ as an internal reference. A positive chemical shift denotes a resonance occurring downfield from internal standars. The reaction products were analyzed by GC Hewlett-Packard HP 5890 Series 2 Chromatograph using a 10 m x 0.53 column. GC/MS data were obtained on a Hewlett-Packard HP 6890 Series Gas Chromatograph equipped with a HP5973 MSD.

Methyl 3-(4,4,4-trifluoro-3-oxo-1-butenyl)-acrylate (2a) (mixture of cis/trans isomers). 1,1,1-Trifluoro-3-buten-2-one (69.5 g, 0.5 mol), 3-methoxymethylacrylate (58 g, 0.5 mol) and NaOMe (27 g, 0.5 mol) were dissolved in 250 ml of N-methylpyrolidone. Vacuum 150 mbar was applied to the flask and the reaction mixture was stirred under reduced pressure at 70 °C for 2 h. Volatile products, mainly methanol, were condensed in the cold trap. The reaction mixture was cooled, diluted with water and the formed precipitate was filtered off, washed and dried. Yield: 75 g (88 %), m.p.110–114 °C MS: m/z 223 (M+).

3-[(4,4,4-Trifluoro-3-oxo-1-butenyl) amino]-2-propenenitrile (2b). 1,1,1-Trifluoro-3-buten-2-one (69.5 g, 0.5 mol), 3,3-dimethoxypropionitrile (60.3 g, 0.5 mol) and NaOMe (0.5 mol) were dissolved in 250 of N-methylpyrolidone. Vacuum 150 mbar was applied to the flask and the reaction mixture was stirred under reduced pressure at 70 °C for 1 h. Volatile products, mainly methanol, were condensed in the trap. The reaction mixture was then cooled, diluted with water and the formed precipitate was filtered off, washed and dried.

Yield: 85.5 g (90 %), m.p. 123–127 °C. ^{19}F NMR ($CDCl_3$): δ –77.6 (*s*), –77.5 (*s*), –77.3 (*s*), –77.2 (*s*) ppm. The solid (mixture of four isomers) was purified using column chromatography on silica gel (eluent hexane/ethyl acetate). Two fractions were collected.

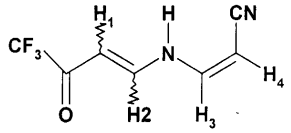
Fraktion A. Z/E and E/E isomers:



^{1}H NMR (DMSO d_6) δ: 5.83 (*d*, *J*=13 Hz, H_1), 5.72 (*d*, *J*=8 Hz, H_1),: 7.88 (*d*, *J*=13 Hz, H_2), 7.48 (*d*, *J*=8 Hz, H_2), 7.48 (*d*, *J*=14 Hz, H_3), 7.45 (*d*, *J*=14 Hz, H_3), 5.41 (*d*, *J*=14 Hz, H_4), 5.12 (*d*, *J*=14 Hz, H_4). MS: *m/z* 190 (M^+).

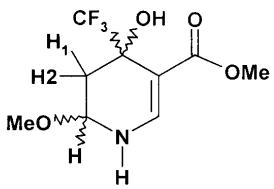
Found, %: C 44.58, H 3.01, F 30.1. Anal. calc. for $C_7H_5F_3N_2O$, %: C 44.22, H 2.65, F 29.98.

Fraktion B. Z/Z and E/Z isomers:



^{1}H NMR (DMSO d_6) δ: 5.90 (*d*, *J*=13 Hz, H_1), 5.72 (*d*, *J*=8 Hz, H_1), 7.91 (*d*, *J*=13 Hz, H_2), 7.51 (*d*, *J*=8 Hz, H_2), 7.28 (*d*, *J*=8 Hz, H_3), 7.44 (*d*, *J*=9 Hz, H_3), 4.91 (*d*, *J*=8 Hz, H_4), 4.82 (*d*, *J*=9 Hz, H_4). MS: *m/z* 190 (M^+).

Methyl 4-hydroxy-6-methoxy-4-(trifluoromethyl)-1,4,5,6-tetrahydro-3-pyridincarboxylate (4a). 19 g (0.1 mol) of methyl 3-(4,4,4-trifluoro-3-oxo-1-butenyl)-acrylate 2a and 1 g of Li_2CO_3 were heated in 200 ml methanol for 6–8 h at 70 °C. The mixture was cooled to 20 °C and the solvent was removed in vacuum. The mixture of both diastereoisomers was separated by column chromatography on SiO_2 using ethyl acetate/heptane as eluent:



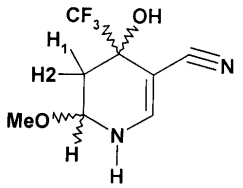
Isomer A. Yield 48 %, m.p. 148–149 °C. ^{1}H NMR ($CDCl_3$) δ: 1.98 (*dm*, *J* = 17 Hz, 1H); 2.68 (*dm*, *J*=17 Hz, 1H), 3.39 (*s*, 3H), 3.73 (*s*, 3H), 4.57 (*m*, 1H), 5.60 (*b.s*, 1H), 6.33 (*s*, 1H), 7.60 (*d*, *J*=7 Hz , 1H). ^{19}F NMR ($CDCl_3$) δ: –81.0 (*s*). MS: *m/z* 255 (M^+).

Found, %: C 42.63, H 5.11. Calc. for $C_9H_{12}F_3NO_4$, %: C 42.36, H 4.74.

Isomer B. Yield 46 %,oil. ^{1}H NMR ($CDCl_3$) δ: 1.96 (*ddq*, *J*=16 Hz, 2 Hz, 1H,); 2.53 (*ddd*, *J*=16 Hz, 5 Hz, 1.5 Hz,1H), 3.42 (*s*, 3H), 3.71(*s*, 3H), 4.57 (*m*, 1H), 5.60 (*b.s*, 1H), 6.63 (*s*, 1H), 7.60 (*d*, *J*=7 Hz, 1H). ^{19}F NMR ($CDCl_3$) δ: –81.0 (*s*). MS: *m/z* 255 (M^+).

4-Hydroxy-6-methoxy-4-(trifluoromethyl)-1,4,5,6-tetrahydro-3-pyridinecarbonitrile (4b). To the solution of (1.9 g,0.01 mol) of 3-(4,4,4-trifluoro-3-oxo-1-butenyl)-2-propenenitrile in 20 ml methanol 0.2 g NaOMe was added. A mixture was stirred for 10–14 h at RT and a solvent was removed in va-

cuum. The solid was purified by crystallisation from ethyl acetate to give 1.7 g (90 %) of 4b as a mixture of two isomers. M.p. 118–124 °C.



Isomer A. ^{1}H NMR (CD_3OD) δ: 1.72 (*m*, 1H), 1.91 (*m*, 1H), 3.22 (*s*, 3H), 4.52 (*m* ,1H), 6.88 (*s*, 1H). ^{19}F NMR ($CDCl_3$) δ: –80.76. MS: *m/z* 222 (M^+).

Isomer B. ^{1}H NMR: (CD_3OD) δ: 1.76 (*m*,1H), 1.94 (*m*, 1H), 3.23 (*s*, 3H), 4.56 (*m*, 1H), 6.89 (*s*, 1H). ^{19}F NMR ($CDCl_3$) δ: –80.79. MS: *m/z* 222 (M^+).

Methyl-4-trifluoromethyl-3-pyridincarboxylate (5a). Methyl 3-(4,4,4-Trifluoro-3-oxo-1-butenyl)-acrylate (19 g, 0.1 mol) of and of Li_2CO_3 (1 g) were heated in 200 ml of methanol at 60 °C for 6–8 h. The mixture was cooled to 20 °C and 10 ml of HCl (37 %) was added. The solvent was removed in vacuum 200 mbar and the residue was extracted with diethyl ether and washed with water. The solvent was evaporated and the product purified via vacuum distillation.Yield 14 g, 81 % b.p. 78–82 °C/ 15 mbar.

^{1}H NMR ($CDCl_3$) δ: 9.07 (*s*, 1H), 8.89 (*d*, *J*= 4 Hz, 1H,), 7.62 (*d*, *J*=4 Hz,1H), 3.10 (*s*, 3H,). ^{19}F NMR ($CDCl_3$) δ: –62.4 (*s*). MS: *m/z* 205 (M^+).

4-Ttrifluoromethyl-3-pyridinecarbonitril (5b). Methyl 3-(4,4,4-trifluoro-3-oxo-1-butenyl)-acrylate (19 g, 0.1 mol) of and Li_2CO_3 (1 g) were heated in 200 ml of methanol at 60 °C for 6–8 h. The mixture was cooled to 20 °C and 10 ml of HCl (37 %) was added. The solvent was then removed in vacuum and the residue was extracted with diethyl ether and washed with water. The solvent was evaporated and the product purified via vacuum distillation. Yield 14 g, 81 %, b.p. 80–82 °C/ 18 mbar.

^{1}H NMR ($CDCl_3$) δ: 8.87 (*s*, 1H), 8.81 (*d*, *J*=5 Hz, 1H), 7.51 (*d*, *J*=5 Hz, 1H). ^{19}F NMR ($CDCl_3$) δ: –64.5 (*s*)[8].

4-Trifluoromethylnicotinamide (7). Method A. 3-[(4,4,4-Trifluoro-3-oxo-1-butenyl)amino]-2-propennitrile (19 g, 0.1 mol) was added slowly to the 50 ml of sulphuric acid while maintaining a temperature below 35 °C. The reaction mixture was stirred for 10 h at ambient temperature and poured on 200 g of ice. The pH was adjusted to 8 by adding of NH_4OH solution, the formed precipitate was filtered off and washed with water to give 16.1 g (85 %) of the amide with , m.p. 167–168 °C and purity w.w. % (HPLC) 98 %.

^{1}H NMR (DMSO-d_6): δ: 8.85 (*s*,1H), 8.78 (*d*, *J*=4 Hz, 1H), 8.16 (*b.s*, 1H), 7.83 (*b.s*, 1H), 7.79 (*d*, *J*=4 Hz, 1H). ^{19}F NMR ($CDCl_3$) δ: –60.2.

Method B. 4-Ttrifluoromethyl-3-pyridine-carbonitrile (17 g, 0.1 mol) was heated in 100 ml water containing 2 g of Na_2CO_3 at 100 °C for 6 h. The mixture was cooled to 20 °C and white solid was filtered off to give 18.6 g (98 %) of 4-trifluoromethylnicotinamide.

N-Chloro-4-trifluoromethylnicotinamide hydrochloride (8). In a 0.5 l four-necked flask 150 g of 5 % HCl and 50 g of 4-trifluoronicotinamide were charged, the mixture was stirred at room temperature for 15 min and 20 g of Cl_2 were then introduced such that the chlorine was taken up completely. After addition of about 10 g of chlorine, the starting material dissolved and the product precipitated as a white solid. Crystalline product was filtered off and washed once with 30–40 ml of ice-cold water and dried at RT. This gave 58 g of 8 (92 % yield), m.p. 150–152 °C (dec.), active chorine 13.7 %. The product was treated with $NaHCO_3$ at 10 °C to give N-chloro-4-trifluoromethylnicotinamide with m.p. 140–141 °C [19].

Found, %: C 37.01, Cl 15.98 Calc. for $C_7H_4ClF_3N_2O$, %: C 37.44, Cl 15.79.

N-(Diphenyl–λ^4-sulfanylidene)-4-(trifluoromethyl) nicotinamide (9). A solution of of diphenylsulphide (1.86 g, 0.01 mol) and triethylamine (2.02 g, 0.02 mol) in 10 ml chlorbenzene was added dropwise to a solution of N-Chloro-4-trifluoromethyl-nicotinamide hydrochloride (2.6 g, 0.01 mol). The reaction mixture was stirred at 20 ° C for 4 h, the precipitate (triethylamine hydrochloride) was filtered off and the filtrate was concentrated under reduced pressure. The solid was collected and washed with hexane. Yield 3.3 g (90 %), m.p. 94–95 ° C[18].

РЕЗЮМЕ. Розроблено прості і зручні методи синтезу таких біологічно активних похідних 4-трифлуорометилнікотинової кислоти як аміди, естери і нітрил.

РЕЗЮМЕ. Разработаны простые и удобные методы синтеза таких биологически активных производных 4-трифторметилникотиновой кислоты, как амиды, эфиры и нитрил.

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