Synthesis of derivatives of 4-amino-2-trifluoromethylnicotinic acid

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The method for the synthesis of ethyl 4-R-amino-2-trifluoromethylnicotinates from a diphenylboron complex of ethyl 2-acetyl-3-amino-4,4,4-trifluorobut-2-enoate was developed.

Key words: diphenylboron chelates, ethyl 4-R-amino-2-trifluoromethylnicotinates, 3-benzyl-5-trifluoromethylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one, dimethylformamide dimethyl acetal.

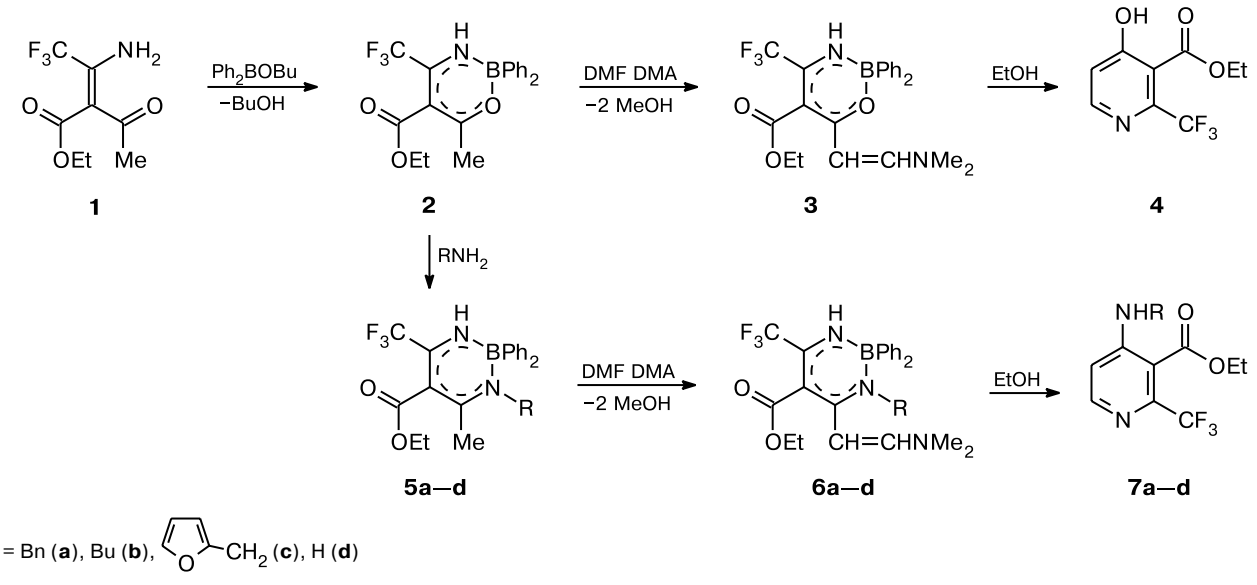
Derivatives of 2- and 4-aminonicotinic acids attract attention not only as potential biologically active substances and medicines,[1—5] but also as convenient starting reagents for construction of nitrogen-containing bicyclic systems.[6—9] However, the number of papers devoted to 2-aminonicotinic acid and its esters is significantly higher than that concerned with their less accessible 4-amino isomers (ethyl 4-aminonicotinate is usually synthesized in five steps from 3-methyl-4-nitropyridine 1-oxide[8—9]).

Recently,[10] we proposed a comparatively simple route to ethyl 4-amino-2,6-diarylnicotinates starting from nickel chelates and aroylacetonitriles. The goal of the present work was to obtain 4-aminonicotinic acid derivatives containing a trifluoromethyl substituent in the pyridine ring, because such reagents are of interest for use in the synthesis of fused heterocycles with a potential biological activity.

Earlier, we found[11] that diphenylboron chelate **2** easily prepared from ethyl 2-acetyl-3-amino-4,4,4-trifluorobut-2-enoate (**1**) reacts under mild conditions with dimethylformamide dimethyl acetal (DMF DMA) to give condensation product **3**, which can be converted through alcoholysis into ethyl 4-hydroxy-2-trifluoromethylnicotinate (**4**). It was also noted that heating of chelate **2** with benzylamine yields β-diiminate complex **5a** (Scheme 1).

In continuation of those studies, chelates **5b,c** were obtained by reactions of compound **2** with *n*-butylamine and 2-furfurylamine in boiling benzene (a slight excess of the primary amine was used). An analogous reaction with a solution of ammonia in toluene in a sealed tube at 120 °C afforded complex **5d** in 84% yield.

Scheme 1



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Diphenylboron chelates **5a—d** reacted with DMF DMA in boiling toluene to give the corresponding complexes **6a—d**. Without isolation, they were heated with ethanol in a sealed tube at 120 °C to form, *via* the opening of the boron-containing ring, ethyl 4-R-amino-2-trifluoromethylpyridine-3-carboxylates **7a—d** in 37—60% yields. The esters obtained are crystalline compounds, which are well soluble in chloroform, benzene, and ether and poorly soluble in hexane. Their mass spectra contain molecular ion peaks and their ^{1}H NMR spectra in $CDCl_3$ show doublet signals at δ 6.65—6.78 for the H(5) proton and at δ 8.26—8.32 for the H(6) proton of the pyridine ring. The IR spectrum of pyridine derivative **7d** contains absorption bands at 3500, 3390 (NH_2), and 1710 cm^{-1} (C=O).

Ester **7d** was used to construct a bicyclic system. When heated with benzylamine, it yielded amide **8** which, through refluxing with DMF DMA, afforded 3-benzyl-5-trifluoromethylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**9**).

The mass spectrum of compound **9** contains a molecular ion peak with $[305]^+$. Its IR spectrum shows an absorption band at 1688 cm^{-1} (C=O). Structure **9** was also confirmed by ^{1}H NMR data.

Scheme 2

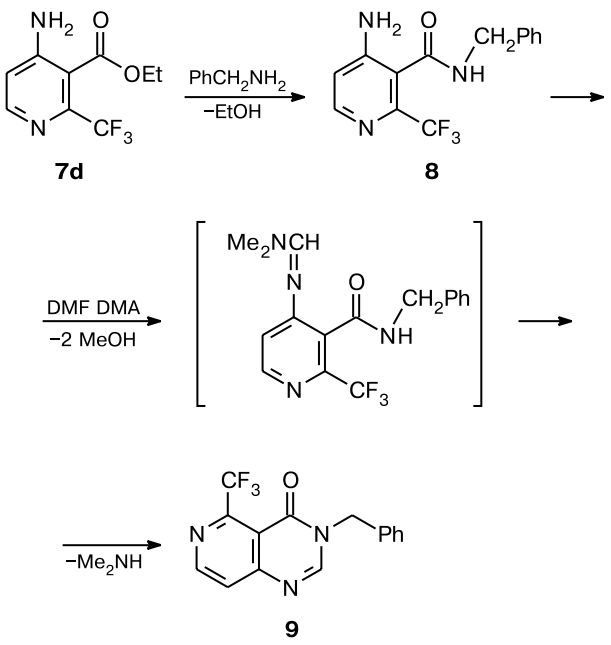

Table 1. Yields, physicochemical properties, and ^{1}H NMR data for compounds **5**, **7**, **8**, and **9**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Molecular formula	^{1}H NMR ($CDCl_3$) δ, *J*/Hz
			C	H	N		
5b	86	69—70	65.14 64.86	6.50 6.30	6.20 6.30	$C_{24}H_{28}BF_3N_2O_2$	0.57 (t, 3 H, Me); 0.80—1.10 (m, 4 H, 2 CH_2); 1.26 (t, 3 H, Me, *J* = 6.9); 2.53 (s, 3 H, Me); 3.32 (t, 2 H, CH_2N, *J* = 6.5); 4.15 (q, 2 H, CH_2O, *J* = 6.9); 6.48 (br.s, 1 H, NH); 7.20—7.40 (m, 10 H, 2 Ph)
5c	79	91—92	64.11 64.10	5.16 5.13	6.06 5.98	$C_{25}H_{24}BF_3N_2O_3$	1.27 (t, 3 H, Me, *J* = 6.9); 2.68 (s, 3 H, Me); 4.15 (q, 2 H, CH_2O, *J* = 6.9); 4.60 (s, 2 H, CH_2N); 5.27 (d, 1 H, H(3), *J* = 3.5); 6.10 (dd, 1 H, H(4), *J* = 1.6, *J* = 3.5); 6.62 (br.s, 1 H, NH); 7.15—7.10 (m, 11 H, 2 Ph+H(5))
5d	83.5	170—171	61.62 61.85	5.09 5.19	7.27 7.21	$C_{20}H_{20}BF_3N_2O_2$	1.30 (t, 3 H, Me, *J* = 6.9); 2.51 (s, 3 H, Me); 4.18 (q, 2 H, CH_2O, *J* = 6.9); 6.80 (br.s, 1 H, NH); 6.86 (br.s, 1 H, NH); 7.21—7.53 (m, 10 H, 2 Ph)
7a	40	76—77	59.32 59.26	5.15 4.83	8.46 8.69	$C_{16}H_{15}F_3N_2O_2$	1.39 (t, 3 H, Me, *J* = 6.8); 4.39 (q, 2 H, CH_2O, *J* = 6.8); 4.40 (d, 2 H, CH_2N, *J* = 5.5); 6.63 (d, 1 H, H(5), *J* = 6.1); 7.00 (br.s, 1 H, NH); 7.25—7.50 (m, 5 H, Ph); 8.26 (d, 1 H, H(6), *J* = 6.1)
7b	40	19—20	54.01 53.79	6.03 5.86	9.33 9.65	$C_{13}H_{17}F_3N_2O_2$	0.98 (t, 3 H, Me, *J* = 6.9); 1.30—1.50 (m, 4 H, 2 CH_2); 1.65 (t, 3 H, Me, *J* = 6.9); 3.20 (t, 2 H, CH_2N, *J* = 6.5); 4.38 (q, 2 H, CH_2O, *J* = 6.9); 6.50 (br.s, 1 H, NH); 6.65 (d, 1 H, H(5), *J* = 6.1); 8.28 (d, 1 H, H(6), *J* = 6.1)
7c	37	70—71	53.61 53.50	4.39 4.14	8.97 8.92	$C_{14}H_{13}F_3N_2O_3$	1.39 (t, 3 H, Me, *J* = 6.8); 4.37 (q, 2 H, CH_2O, *J* = 6.8); 4.42 (d, 2 H, CH_2N, *J* = 6.0); 6.28 (d, 1 H, H(3´), *J* = 3.5); 6.35 (dd, 1 H, H(4´), *J* = 1.6, *J* = 3.5); 6.78 (d, 1 H, H(5), *J* = 6.1); 6.90 (br.s, 1 H, NH); 7.40 (d, 1 H, H(5´), *J* = 1.6); 8.32 (d, 1 H, H(6), *J* = 6.1)

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Molecular formula	^{1}H NMR ($CDCl_3$) δ, *J*/Hz
			C	H	N		
7d	60	82—83	46.16 46.15	4.04 3.84	11.90 11.96	$C_9H_9F_3N_2O_2$	1.38 (t, 3 H, Me, *J* = 6.9); 4.38 (q, 2 H, CH_2O, *J* = 6.9); 5.58 (br.s, 2 H, NH_2); 6.69 (d, 1 H, H(5), *J* = 6.0); 8.21 (d, 1 H, H(6), *J* = 6.0)
8	68	180—181	56.88 56.94	4.26 4.06	14.22 14.23	$C_{14}H_{12}F_3N_3O$	4.45 (d, 2 H, CH_2N, *J* = 6.0); 6.20 (br.s, 2 H, NH_2); 6.80 (d, 1 H, H(5), *J* = 5.9); 7.18—7.50 (m, 5 H, Ph); 8.10 (d, 1 H, H(6), *J* = 5.9); 8.95 (t, 1 H, NH, *J* = 5.0)
9	60	131—132	58.90 59.01	3.26 3.27	13.47 13.77	$C_{15}H_{10}F_3N_3O$	5.23 (s, 2 H, CH_2); 7.35—7.45 (m, 5 H, Ph); 7.75 (d, 1 H, H(7), *J* = 5.5); 8.29 (s, 1 H, H(2); 8.88 (t, 1 H, H(8), *J* = 5.5)

Experimental

^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer (250.13 MHz). IR spectra were recorded on a Perkin-Elmer 577 instrument. Mass spectra were recorded on a Varian MAT-311A instrument.

Diphenylboron complexes **2** and **5a** were prepared as described by us earlier.[11]

The yields and physicochemical and spectral characteristics of all the compounds obtained are given in Table 1.

Diphenylboron complexes of ethyl 2-(1-alkyliminoethyl)-3-amino-4,4,4-trifluorobut-2-enoates 5b,c. A mixture of chelate **2** (1.0 g, 2.5 mmol) and an amine (3.5 mmol) in 15 mL of benzene was refluxed for 3 h and concentrated *in vacuo*. Crystallization of the residue from hexane gave chelates **5b,c**.

Diphenylboron complex of ethyl 3-amino-4,4,4-trifluoro-2-(1-iminoethyl)but-2-enoate (5d). A mixture of chelate **2** (3.0 g, 7.7 mmol) and 0.2 *M* NH_3 (62 mL, 12 mmol) in toluene was heated in a sealed tube at 120 to 140 °C for 15 h. The reaction mixture was concentrated *in vacuo*. Recrystallization of the residue from hexane gave chelate **5d** (2.5 g).

Ethyl 4-R-amino-2-trifluoromethylnicotinates 7a—d (general procedure). A mixture of complex **5a—d** (2.6 mmol) and DMF DMA (0.4 mL, 3.1 mmol) in 15 mL of toluene was refluxed for 10 h (monitoring by TLC) and concentrated *in vacuo*. Ethanol (20 mL) and xylene (10 mL) were added. The resulting mixture was heated in a sealed tube at 115 to 120 °C for 5 h and then concentrated *in vacuo*. The residue was chromatographed on SiO_2 with benzene as an eluent to give nicotinates **7a—d**.

***N*-Benzyl-4-amino-2-trifluoromethylpyridine-3-carboxamide (8).** Compound **7d** (0.2 g, 0.85 mmol) was refluxed in 2 mL of benzylamine for 5 h, cooled to 20 °C, and diluted with hexane (3 mL). The oil that formed was separated and benzene (3 mL) was added. The crystals that formed were filtered off and washed with benzene (10 mL) and hexane (10 mL) to give amide **8** (0.17 g).

3-Benzyl-5-trifluoromethylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (9). A mixture of amide **8** (0.12 g, 0.4 mmol) and DMF DMA (0.1 mL, 0.8 mmol) in 5 mL of xylene was refluxed for 5 h and concentrated *in vacuo*. The residue was eluted with benzene through a thin layer of SiO_2 to give compound **9** (0.075 g).

References

1. R. J. Flower, *Pharmacol. Rev.*, 1974, **26**, 33.
2. E. Lukevits, *Khim. Geterotsikl. Soedin.*, 1995, 723 [*Chem. Heterocycl. Compd.*, 1995 (Engl. Transl.)].
3. R. A. Akhundov, L. A. Zhmurenko, O. M. Glozman, T. A. Voronina, and V. A. Zagorevskii, *Khim.-Farm. Zh.*, 1986, **20**, 48 [*Pharm. Chem. J.*, 1986, **20** (Engl. Transl.)].
4. D. Pancechowska-Ksepko, J. Sawiewicz, and W. Monowska, *Pol. J. Pharmacol. Pharm.*, 1975, **27**, 637.
5. K. Konna, K. Hayana, H. Shirahama, H. Soito, and T. Metsumoto, *Tetrahedron*, 1982, **38**, 3281.
6. A. Sh. Oganisyan, A. S. Noravyan, and S. A. Vartanyan, *Usp. Khim.*, 1987, **56**, 2001 [*Russ. Chem. Rev.*, 1987, **56** (Engl. Transl)].
7. V. P. Litvinov, S. B. Roman, and B. D. Dyachenko, *Usp. Khim.*, 2000, **69**, 218 [*Russ. Chem. Rev.*, 2000, **69**, 201 (Engl. Transl)].
8. A. G. Ismail and D. G. Wibberley, *J. Chem. Soc. C*, 1967, 2613.
9. Zh.-L. Zhou, J. M. Navratil, S. X. Cai, E. R. Whittemore, S. A. Espita, J. E. Hawkinson, M. Tran, R. M. Woodwara, E. Weber, and J. F. Keana, *Bioorg. Med. Chem.*, 2001, **9**, 2061.
10. V. A. Dorokhov, A. V. Vasil´ev, S. V. Baranin, and A. S. Vorushilov, *Izv. Akad. Nauk, Ser. Khim.*, 2003, 1947 [*Russ. Chem. Bull., Int. Ed.*, 2003, **52**, 2057].
11. V. A. Dorokhov, L. S. Vasil´ev, F. E. Surzhikov, and V. S. Bogdanov, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 1329 [*Russ. Chem. Bull.*, 1995, **44**, 1283 (Engl. Transl)].

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