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Synthesis of 2-(polyfluoromethyl)pyrimido[1,2-*a*]benzimidazole-4-carbaldehyde derivatives

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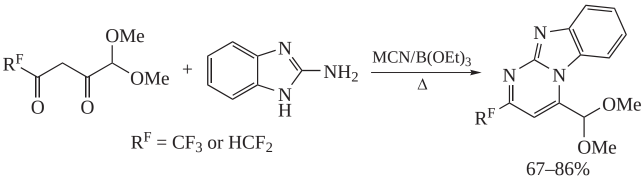
A simple and efficient synthesis of 2-R^F-pyrimido[1,2-*a*]benzimidazole-4-carbaldehyde derivatives comprises the reaction between 3-(polyfluoroacetyl)pyruvaldehyde dimethyl acetals and 2-aminobenzimidazole. The effects of fluorinated substituents in 3-(polyfluoroacetyl)pyruvaldehyde dimethyl acetals and the reaction conditions on regiochemical outcome of this reaction have been estimated.



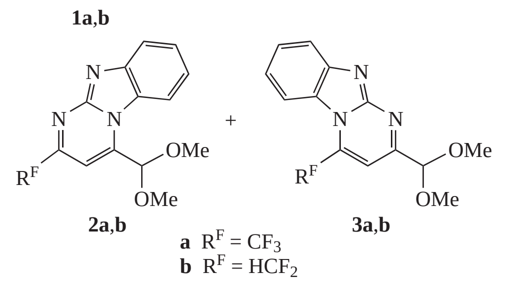
Azolopyrimidines and their fused analogues are of considerable interest due to their wide spectrum of biological activities. Indeed, a number of pyrimido[1,2-*a*]benzimidazoles proved to exhibit antimicrobial,[1] antioxidant,[2] antineurodegenerative,[3] immunotropic,[4] and antiproliferative[5] activities.

Introduction of fluorinated substituents into organic molecules appears to be an effective tool to change their physical and chemical properties, as well as biological activity.[6] A few examples of pyrimido[1,2-*a*]benzimidazoles bearing a fluorinated alkyl group in the pyrimidine ring have been described so far.[7] Compounds of this family exhibit herbicide[7(*a*)] and DNA-topoisomerase I enzyme inhibitor[7(*f*)] activities. Pyrimidobenzimidazoles bearing a fluoroalkyl group (usually trifluoromethyl) have been obtained by reacting 2-aminobenzimidazole with fluoroalkylated β-dicarbonyl compounds,[7(*a*)] 3-trifluoroacetylated lactams,[8] 4-trifluoroacetyl-2,3-dihydropyrroles,[9] β-trifluoroacetylvinyl sulfones,[7(*d*)] and polyfluoroacyl alkoxy enones.[7(*b*),(*f*)] However, further modifications of these compounds were not performed. Therefore, introduction of a versatile functional group into the structure of fluorinated pyrimidobenzimidazoles can be regarded as a useful approach to tune their biological activity.

Recently we have described a new functionalized fluorinated building block containing adjacent 1,3-dicarbonyl and acetal fragments, namely 3-(polyfluoroacetyl)pyruvaldehyde dimethyl acetals [1-(polyfluoromethyl)-4,4-dimethoxybutane-1,3-diones] **1a**,**b**.[10] The dimethyl acetal group in compounds **1a**,**b** provides wide opportunities for modifications of heterocyclic compounds prepared by reaction of 1,3-dicarbonyl moiety with *N*,*N'*-binucleophiles. In this communication, we report the regioselective synthesis of dimethyl acetals, hydrates, and semicarbazones of 2-polyfluoroalkyl-substituted pyrimido[1,2-*a*]benzimidazole-4-carbaldehydes.

We have found that 1,1,1-trifluoro-5,5-dimethoxypentane-2,4-dione **1a** reacted regioselectively with 2-aminobenzimidazole in refluxing methanol to give a mixture of dimethyl acetals of 2-CF$_3$-substituted pyrimido[1,2-*a*]benzimidazole-4-carbaldehyde **2a** and regioisomeric 4-CF$_3$-substituted pyrimido[1,2-*a*]benzimidazole-2-carbaldehyde **3a** in a ratio of ~91 : 9 (^{19}F NMR data for the crude reaction mixture, Scheme 1, Table 1, entry 1).

Further on, we have found that pyrimido[1,2-*a*]benzimidazole **2a** is formed nearly regioselectively when the reaction was carried out either in acetonitrile, or in the presence of 3 equiv. of triethyl



Scheme 1

Table 1 Influence of reaction conditions on the **2** : **3** ratio and yields of the products.

Entry	Diketone	Solvent	*T*/°C	*t*/h	Ratio of **2** : **3**[a]	Isolated yields[b] (%)
1	**1a**	MeOH	64	6	91 : 9	24
2	**1a**	MeCN	82	6	95 : 5	60
3	**1a**	MeCN/B(OEt)$_3$	82	6	98 : 2	70 (67)
4	**1a**	CF$_3$CH$_2$OH	78	6	60 : 40	55
5	**1a**	(CF$_3$)$_2$CHOH	59	6	59 : 41	62
6	**1a**	AcOH	82	3	74 : 26	45
7	**1a**	AcOH	116	0.5	69 : 31	32
8	**1b**	MeCN	82	6	55 : 45	86
9	**1b**	MeCN/B(OEt)$_3$	82	6	95 : 5	92 (86)
10	**1b**	CF$_3$CH$_2$OH	78	6	45 : 55	90
11	**1b**	(CF$_3$)$_2$CHOH	59	6	45 : 55	91

[a] Based on the ^{19}F NMR data for crude reaction mixtures. [b] Mixture of compounds **2** and **3** after column chromatography, and pure **2** in parentheses.

borate (Table 1, entries 2 and 3). Previously, we have shown that the use of trialkyl borates was effective in the selective amination of fluorinated 1,3-diketones with 1,2-diaminobenzene.[11] The application of triethyl borate in the reaction under study increased its yield by 10% and improved the regioselectivity to some extent, thus enabling us to isolate product **2a** in 67% yield.[†]

It is known that the use of 2,2,2-trifluoroethanol and 1,1,1,3,3,3-hexafluoropropan-2-ol as solvents can dramatically change the regioselectivity of reactions between fluorinated 1,3-diketones and substituted hydrazines.[12] When we carried out the reactions in these fluorinated alcohols, the fraction of **3a** was increased up to 40% (see Table 1, entries 4 and 5). However, enriched in **3a** sample (~90%) was obtained in only 9% yield after double chromatography.[‡] Noteworthy, yields of the reaction products and fraction of **3a** in the reaction mixtures were lower when acetic acid was used as solvent (entries 6 and 7).

The most suitable conditions were applied to react 1,1-difluoro-5,5-dimethoxypentane-2,4-dione **1b** with 2-aminobenzimidazole (see Table 1, entries 8–11). Interestingly, this reaction was not regioselective in acetonitrile (entry 8), whereas application of triethyl borate provided a good regioselectivity for the heterocyclization (entry 9) when pure 2-HCF_2-substituted pyrimido[1,2-*a*]benzimidazole-4-carbaldehyde dimethyl acetal **2b** was obtained in 86% yield after a simple crystallization.[†] Regioisomeric 4-HCF_2-substituted pyrimido[1,2-*a*]benzimidazole-2-carbaldehyde dimethyl acetal **3b** better formed in fluorinated alcohols was isolated in 36% yield by chromatography followed by recrystallization (entries 10 and 11).[‡]

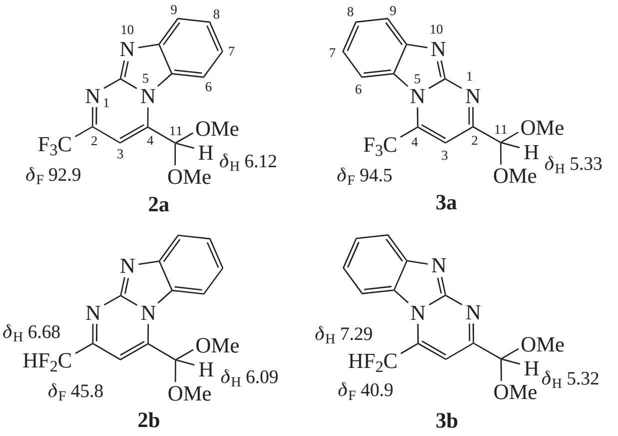


Figure 1 Diagnostic chemical shifts (in ppm) of regioisomeric pyrimido-[1,2-*a*]benzimidazoles **2** and **3**.

The structures of pyrimido[1,2-*a*]benzimidazoles **2** and **3** were determined by elemental analysis, ^{1}H, ^{19}F, ^{13}C and ^{15}N NMR spectroscopy, and unambiguously assigned on the basis of 2D NMR experiments ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC, ^{1}H-^{15}N HMBC, and ^{1}H-^{1}H NOESY (Figure 1). The most notable differences between isomers **2** and **3** have been manifested in 2D ^{1}H-^{15}N HMBC experiments. In the NMR spectra of compounds **2a**,**b**, protons H-6 and H-11 correlate with the same upfield nitrogen N-5 (δ_{N} 170–172 ppm), while in the NMR spectra of **3a**,**b** cross-peaks (H-11, N-1) and (H-6, N-5) are observed. The NOESY experiments for compounds **2a**,**b** have revealed links between H-11 and OMe protons and H-6 of the benzene ring. In the ^{1}H NMR spectra of isomers **2** ($CDCl_3$), singlets for the acetal proton H-11 are located at 6.09–6.12 ppm, whereas the corresponding signals for regioisomers **3** are shifted upfield (δ_{H} 5.32–5.3 ppm). This difference can be explained by a deshielding effect of the benzimidazole fragment in case of compounds **2**. Additionally, in the ^{1}H NMR spectrum of **3b**, the diagnostic triplet of HCF_2-group proton is more deshielded (δ_{H} 7.29 ppm) in comparison with that of **2b** (δ_{H} 6.68 ppm). In the ^{19}F NMR spectrum of **2a**, the CF_3 group appears as a singlet at δ_{F} 92.9 ppm. In case of regioisomer **3a**, the signal of the same fluorinated group is shifted downfield (δ_{F} 94.5 ppm) and appears as a doublet with small J_{HF} 2.2 Hz. In ^{19}F NMR spectra of **2b** and **3b**, the doublets for the HCF_2 group were observed at 45.8 and 40.9 ppm, respectively. In the

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[†] *Regioselective synthesis of 2-R^F-pyrimido[1,2-*a*]benzimidazole-4-carbaldehyde dimethyl acetals* **2a**,**b**. Compounds **1** (1 mmol), 2-aminobenzimidazole (1.05 mmol, 0.140 g) and $B(OEt)_3$ (3 mmol, 0.438 g) were refluxed in MeCN (30 ml) for 6 h. The mixture was cooled and diluted with water (100 ml). The resulting precipitate was filtered off, washed with water (3 × 10 ml), dried in air, and recrystallized from hexane to give corresponding product **2**.

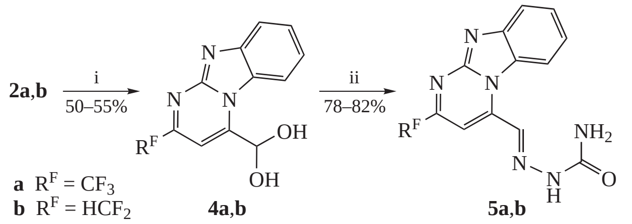
*2-Trifluoromethyl-4-(dimethoxymethyl)pyrimido[1,2-*a*]benzimidazole* **2a**. Yellow powder, yield 0.21 g (67%), mp 141–142 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.48 (s, 6 H, 2 OMe), 6.13 (s, 1H, H-11), 7.49 (ddd, 1H, H-7, J 8.6, 7.2, 1.1 Hz), 7.52 (s, 1H, H-3), 7.63 (ddd, 1H, H-8, J 8.2, 7.2, 1.0 Hz), 8.05 (d, 1H, H-9, J 8.2 Hz), 8.27 (d, 1H, H-6, J 8.6 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ: 92.87 (s, CF_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 53.22 (s, OMe), 96.63 (C^{11}), 101.51 (q, C^3, ${}^{3}J_{\mathrm{CF}}$ 1.5 Hz), 116.68 (C^6), 120.26 (q, CF_3, ${}^{1}J_{\mathrm{CF}}$ 276.1 Hz), 120.56 (C^9), 123.70 (C^7), 126.58 (C^{5a}), 127.33 (C^8), 144.80 (C^{9a}), 148.30 (C^4), 149.14 (C^{10a}), 151.46 (q, C^2, ${}^{2}J_{\mathrm{CF}}$ 37.2 Hz). ^{15}N NMR (50 MHz, $CDCl_3$) δ: 171.9 (N^5), 223.1 (N^{10}), 274.5 (N^1). Found (%): C, 54.11; H, 3.87; N, 13.43; F, 18.22. Calc. for $C_{14}H_{12}F_3N_3O_2$ (%): C, 54.02; H, 3.89; N, 13.50; F, 18.31.

*2-Difluoromethyl-4-(dimethoxymethyl)pyrimido[1,2-*a*]benzimidazole* **2b**. Yellow powder, yield 0.25 g (86 %), mp 128–130°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.47 (s, 6 H, 2 OMe), 6.08 (s, 1H, H-11), 6.68 (t, 1H, HCF_2, ${}^{2}J_{\mathrm{HF}}$ 54.7 Hz), 7.47 (ddd, 1H, H-7, J 8.6, 7.2, 1.3 Hz), 7.50 (s, 1H, H-3), 7.62 (ddd, 1H, H-8, J 8.3, 7.2, 1.1 Hz), 8.06 (d, 1H, H-9, ${}^{3}J$ 8.3 Hz), 8.26 (d, 1H, H-6, ${}^{3}J$ 8.6 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ: 45.90 (d, HCF_2, ${}^{2}J_{\mathrm{FH}}$ 54.7 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 53.14 (s, OMe), 96.93 (C^{11}), 101.18 (C^3), 113.55 (t, HCF_2, ${}^{1}J_{\mathrm{CF}}$ 242.0 Hz), 116.48 (C^6), 120.76 (C^9), 123.16 (C^7), 126.75 (C^8), 126.88 (C^{5a}), 145.29 (C^{9a}), 147.61 (C^4), 150.01 (C^{10a}), 156.43 (t, C^2, ${}^{2}J_{\mathrm{CF}}$ 28.5 Hz). ^{15}N NMR (50 MHz, $CDCl_3$) δ: 170.4 (N^5), 224.5 (N^{10}), 276.4 (N^1). Found (%): C, 57.01; H, 4.40; N, 14.29; F, 12.73. Calc. for $C_{14}H_{13}F_2N_3O_2$ (%): C, 57.34; H, 4.47; N, 14.33; F, 12.96.

[‡] *Preparation of 4-R^F-pyrimido[1,2-*a*]benzimidazole-2-carbaldehyde dimethyl acetals* **3a**,**b**. Compound **1** (2.5 mmol) and 2-aminobenzimidazole (2.63 mmol, 0.350 g) were refluxed in trifluoroethanol (10 ml) for 6 h. The mixture was evaporated to dryness and twice chromatographed (silica gel, eluent $CHCl_3$).

*4-Trifluoromethyl-2-(dimethoxymethyl)pyrimido[1,2-*a*]benzimidazole* **3a**. Yellow powder, yield 0.07 g (9%). Purity ~90% (according to NMR data). Additionally 0.36 g (46%) of **2a** + **3**a mixture was isolated. The total yield was ~55%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.58 (s, 6 H, 2 OMe), 5.33 (s, 1H, H-11), 7.56 (ddd, 1H, H-7, J 8.6, 7.2, 1.3 Hz), 7.65 (s, 1H, H-3), 7.69 (ddd, 1H, H-8, J 8.3, 7.2, 0.9 Hz), 8.11 (dm, 1H, H-6, J 8.6 Hz), 8.17 (d, 1H, H-9, J 8.3 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ: 94.68 (d, CF_3, J_{FH} 2.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 55.45 (s, OMe), 103.51 (q, C^3, ${}^{3}J_{\mathrm{CF}}$ 5.3 Hz), 104.57 (C^{11}), 114.31 (q, C^6, ${}^{5}J_{\mathrm{CF}}$ 5.9 Hz), 119.69 (q, CF_3, ${}^{1}J_{\mathrm{CF}}$ 274.2 Hz), 120.98 (C^9), 123.96 (C^7), 125.90 (C^{5a}), 127.07 (C^8), 135.46 (q, C^4, ${}^{2}J_{\mathrm{CF}}$ 37.9 Hz), 144.34 (C^{9a}), 149.58 (C^{10a}), 162.70 (C^2). ^{15}N NMR (50 MHz, $CDCl_3$) δ: 160.1 (N^5), 224.1 (N^{10}), 284.6 (N^1).

*4-Difluoromethyl-2-(dimethoxymethyl)pyrimido[1,2-*a*]benzimidazole* **3b**. Recrystallization from hexane, yellow powder, yield 0.26 g (36%), mp 149–152 °C. Additionally 0.40 g (54%) of **2b** + **3b** mixture was isolated. The total yield was ~90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.55 (s, 6 H, 2 OMe), 5.30 (s, 1H, H-11), 7.24 (t, 1H, HCF_2, ${}^{2}J_{\mathrm{HF}}$ 52.6 Hz), 7.43 (s, 1H, H-3), 7.46 (ddd, 1H, H-7, J 8.5, 7.3, 1.1 Hz), 7.60 (t, 1H, H-8, J 7.7 Hz), 8.01 (d, 1H, H-6, J 8.5 Hz), 8.04 (d, 1H, H-9, J 8.3 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ: 40.86 (d, HCF_2, ${}^{2}J_{\mathrm{FH}}$ 52.4 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 55.30 (s, OMe), 102.99 (t, C^3, ${}^{3}J_{\mathrm{CF}}$ 7.7 Hz), 104.70 (s, C^{11}), 109.84 (t, HCF_2, ${}^{1}J_{\mathrm{CF}}$ 243.0 Hz), 114.25 (t, C^6, ${}^{5}J_{\mathrm{CF}}$ 4.7 Hz), 120.90 (C^9), 123.40 (C^7), 126.22 (C^{5a}), 126.65 (C^8), 140.26 (t, C^4, ${}^{2}J_{\mathrm{CF}}$ 25.6 Hz), 144.58 (C^{9a}), 149.80 (C^{10a}), 162.91 (C^2). ^{15}N NMR (50 MHz, $CDCl_3$) δ: 163.8 (N^5), 224.1 (N^{10}), 281.3 (N^1). Found (%): C, 57.23; H, 4.37; N, 14.35; F, 13.05. Calc. for $C_{14}H_{13}F_2N_3O_2$ (%): C, 57.34, H, 4.47; N, 14.33; F, 12.96.



Scheme 2 *Reagents and conditions:* i, HCl (aq.), reflux, 1 h, then $NaHCO_3$ (pH 6–7); ii, $NH_2CONHNH_2 \cdot HCl$, AcOH, reflux, 1 h, then AcONa.

^{13}C NMR spectra of isomers **3**, the resonance signal of C-6 carbon is splitted into a quartet ($^5J_{CF}$ 5.9 Hz for **3a**) or triplet ($^5J_{CF}$ 4.7 Hz for **3b**) due to through-space C–F coupling.

Compounds **2a** and **2b**, which were isolated in higher yields and purities, were hydrolyzed and derivatized to demonstrate their synthetic potentials (Scheme 2). The hydrolysis of compounds **2** proved to furnish hydrates of the corresponding heterocyclic aldehydes **4**.[§] The presence of geminal diol moiety was confirmed owing to one-proton triplets ($^3J_{HH}$ 6.8 Hz) at δ 6.55–6.57 ppm and two-proton doublets ($^3J_{HH}$ 6.8 Hz) at δ 7.54–7.61 ppm observed in the ^1H NMR spectra of compounds **4a** and **4b**. The first signal is transformed into a broad singlet after the addition of CD_3COOD, whereas the second one proved to be disappearing. Therefore, these signals can be assigned unambiguously to H-11 and OH protons, respectively. Noteworthy, additional sets of signals with ~6–10% integral intensities were detected in the ^1H and ^{19}F NMR spectra of hydrates **4a** and **4b**, and they were assigned to the corresponding heterocyclic carbaldehydes, since characteristic singlets of the aldehyde group were expected to be observed at δ_H 10.4 ppm.

Compounds **4** proved to undergo decomposition in the course of the dehydration reaction. Nevertheless, they react smoothly with semicarbazide in refluxing acetic acid to afford the corresponding semicarbazones **5a** and **5b** in high yields.[§] Their structures were confirmed by elemental analysis, ^1H, ^{19}F and ^{13}C NMR spectroscopy.

In conclusion, the reaction of 1-polyfluoroalkyl-4,4-dimethoxybutane-1,3-diones with 2-aminobenzimidazole has been accomplished, and an efficient approach to particular derivatives (dimethyl acetal, hydrate, and semicarbazone) of 2-polyfluoroalkyl-substituted pyrimido[1,2-*a*]benzimidazole-4-carbaldehydes has been developed.

This study was performed within framework of the subject AAAA-A19-119011790132-7 of the State target. Analytical studies were carried out using equipment of the Center for Joint Use ‘Spectroscopy and Analysis of Organic Compounds’ at the I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.05.002.

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[§] General remarks, synthesis of hydrates and semicarbazones of 2-R^F-pyrimido[1,2-*a*]benzimidazole-4-carbaldehydes **4** and **5**, and the characterization data for all synthesized compounds are given in Online Supplementary Materials.