Facile Synthesis of Fluorinated Pyrrolo[2,3-*b*]pyridines

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Abstract: With the purpose to synthesize novel ADAs (adenosine deaminase) and IMPDH (inosine 5′-monophosphate dehydrogenase) inhibitors the reaction of 5-amino-1-*tert*-butyl-1*H*-pyrrolo-3-carbonitrile with fluorinated 1,3-biselectrophiles was studied. An efficient and convenient synthetical approach to obtain fluorinated pyrrolo[2,3-*b*]pyridines was developed. *tert*-Butyl protecting group was successfully cleaved by treating of synthesized pyrrolopyridines with concentrated sulfuric acid.

Key words: pyrrol, amine, fluorine, pyridine, annulation, electrophilic aromatic substitution

Nucleosides containing pyrrolo[2,3-*b*]pyridine and pyrrolo[2,3-*d*]pyrimidine ring systems as a nucleobase play a significant role in modern medical chemistry. Since pyrrolo[2,3-*b*]pyridines and pyrrolo[2,3-*d*]pyrimidines were considered as 1,7-deaza and 7-deazapurines, respectively, and their biological activities were recognized to be close to purine one; in the last decades a set of drugs and bioactive molecules containing those two heterocyclic systems appeared on the market.

Recently, several naturally occurring nucleoside antineoplastics,[1] possessing a pyrrolo[2,3-*d*]pyrimidine framework, such as tubercidin (**1**), toyocamycin (**2**), sangivamycin (**3**), and cadeguomycin (**4**, Figure 1) were isolated. Their frequent natural occurrence and unusual biological properties have promoted ample studies toward their synthesis and biological evaluation.[2] Several structurally related deazapurine nucleosides have been synthesized, which have shown antitumor,[3] anti-HIV,[4] and antiviral[5] activities. Triciribine (TCN) came successfully through phase I clinical trial, and it was advanced to phase II studies as a potential antineoplastic agent.[6] Concerning the similar pyrrolopyridines the most significant compound among them is 7-azaindolylcarboxy-*endo*-tropanamide (DF 1012, **5**, Figure 1), which is the selected candidate drug in a new class of non-narcotic antitussive compounds and is actually under investigation in phase II clinical trials.[7]

It became apparent that a variety of C-6-modified purines[8] and their isosteres[9] including pyrrolopyridines[10] and pyrrolopyrimidines[11] were recognized as ADA (adenosine deaminase) inhibitors. Some of them have been synthesized and their pharmaceutical evaluation is currently under investigation.

6-(Trifluoromethyl)-substituted purine analogues are suspected to be a promising scaffold for the elaboration of potential ADA inhibitors.[12] Through the electron-withdrawing CF_3 group the hydration on the position 6 is enabled to form stable hydrates. The CF_3 group is isosterically similar to the amino function,[13] thus 6-hydroxy 6-(trifluoromethyl)purines and their isosteres can be considered as a putative adenosine deamination transition-state mimetic. Coformycin and pentostatin and their derivatives contain a tetrahedral carbon (C-8) bearing a hydroxy group. These naturally occurring ADA inhibitors possess a strong activity (coformycin, $K_i = 1.0 \cdot 10^{-11}$ M; pentostatin, $K_i = 2.5 \cdot 10^{-12}$ M on calf intestine ADA) that is attributed to the extremely tight-binding (nearly irreversible) interaction of those compounds with ADA, mimicking the transition state of ADA activity.[14]

It was shown that the 6-chloro-substituted purine base[15] is dehalogenated by inosine 5′-monophosphate dehydrogenase (IMPDH) and a covalent bond is formed at C-6 with Cys 331.

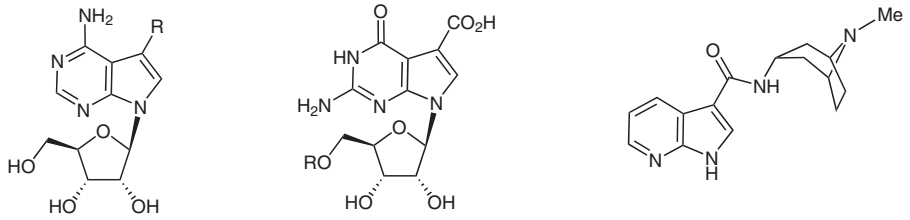

Figure 1 Natural occurring and pharmacoactive pyrrolo[2,3-*d*]pyrimidine and pyrrolo[2,3-*b*]pyridines

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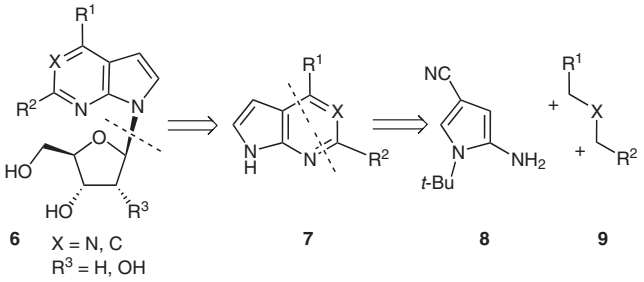
Hence, purines and their analogues bearing polyfluoroalkyl substituents in the positions 2 and 6 should also be considered as potential IMPDH inhibitors, due to the possible formation of the covalent binding with the Cys 331 rest of the active side of the enzyme. We are suspecting that the highly electrophilic C-6 (C-2) atom bearing an electron-withdrawing polyfluoroalkyl group will attack the mercapto function of Cys 331. The stable adduct results in an irreversible enzyme inhibition.

Our primary interests are focused on the design and synthesis of novel ligands for ADA and IMPDH, which would be based on the polyfluoroalkyl containing purines and purine isosteres. The retrosynthetic analysis (Scheme 1) is based on the chemical properties of electron-enriched aminoheterocycles. The heteroannulation of aminopyrroles and polyfluoro-substituted 1,3-CCC/1,3-CNC-biselectrophiles results in the pyrrolo[2,3-*b*]pyridines and pyrrolo[2,3-*d*]pyrimidine with the desired substitution pattern.



Scheme 1 Retrosynthetic analyses

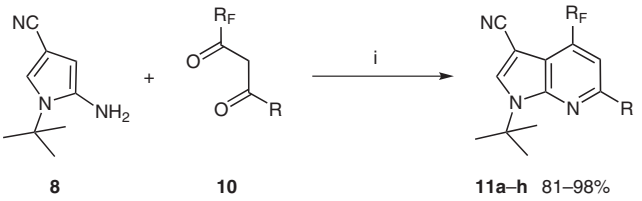
This concept of building up heterocyclic systems has recently gained a wide popularity. Hence, it opens a wide range of practical routes towards fluorinated purine analogues, and a number of small fluorine-containing heterocycles.[16]

The unsubstituted 1*H*-pyrrol-2-amine is hardly accessible and not stable.[17] For our current study the stable and easily accessible 5-amino-1-*tert*-butyl-1*H*-pyrrole-3-carbonitrile was used. The *tert*-butyl protection group and the electron-withdrawing cyano function maintain the stability of this heterocycle. Furthermore, the *tert*-butyl and cyano groups could easily be removed from the pyrrolopyridine derivate.[18]

Further, a glycosylation reaction should be studied with the purpose to couple ribose/2-deoxyribose rests with the fluorinated nucleobase moiety **7**.

In the following, the design and synthesis of novel potential inhibitors of the ADA and IMPDH enzymes family are presented. The practical synthetic route to pyrrolo[2,3-*b*]pyridines, starting from the 5-amino-1-*tert*-butyl-1*H*-pyrrole-3-carbonitrile (**8**) and a number of 1,3-CCC-bis-electrophiles containing a fluoroalkyl group (**10**, **12**, **14**). Previously, methods giving rise to pyrrolo[2,3-*b*]pyridines via annulation of pyridine ring to aminopyrrole moiety have been reported.[18,19]

We have started our attempts with the study of the reaction of the previously mentioned aminopyrrol **8** with polyfluoroalkyl-1,3-diketones **10** (Scheme 2). The studied reaction yields pyrrolo[2,3-*b*]pyridines **11**[20] (Table 1) bearing the fluoroalkyl substituent in the position 4 of the annulated pyridine ring. The cyclocondensation proceeds regioselectively to provide the desired γ-regioisomer; a formation of the α-R_F regioisomer was not observed (^{13}C NMR, ^{19}F NMR).



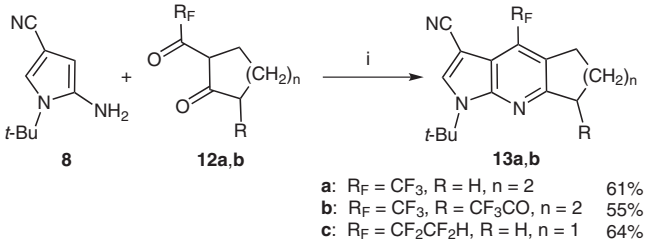
Scheme 2 *Reagents and conditions*: (i) AcOH, reflux under inert atmosphere, 1 h.

Table 1 Yields of Pyrrolo[2,3-*b*]pyridines **11a–i**

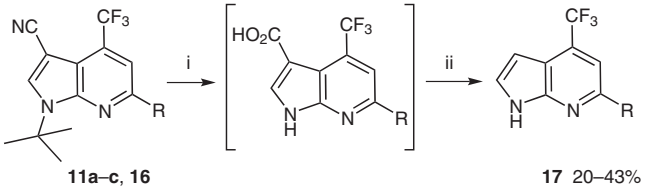
Product	R_F	R	Yield (%)[a]
11a	CF_3	CF_3	89
11b	CF_3	Me	94
11c	CF_3	Ph	88
11d	CF_2H	Me	81
11e	CF_2Cl	Ph	90
11f	C_2F_5	Me	98
11g	CF_2CF_2H	Et	84
11h	$CF_3CF_2CF_2CF_2$	Et	89

[a] Yields refer to pure isolated products.

The cyclic diketones **12** were no exception to the general rule. They have proved to be suitable for the reaction of pyridine ring annulation, which led to the formation of linear 1,5,6,7-tetrahydrocyclopenta[*b*]pyrrolo[3,2-*e*]pyridine and 5,6,7,8-tetrahydro-1*H*-pyrrolo[2,3-*b*]quinolines **13** (Scheme 3). Various solvents were tested as reaction media, the best results have been obtained using acetic acid. Cycloaddition takes place in boiling acetic acid under inert atmosphere of nitrogen for one hour.[21] The studied interaction proceeds quite clean to deliver no byproducts, if the initial diketone and pyrrolamine were analytically pure. An excess of electrophile was removed afterwards in vacuo, and the subsequent purification was not demanded (**11b**,**g**). However, in the case of cyclic diketones **12**, during the examination of the reaction mixture by ^{19}F NMR, a number of byproducts were detected. Attempts to isolate them failed. Formed pyrrolopyridines **11** and **13** could easily be purified by flash chromatography or recrystallized from the appropriate solvent.



Scheme 3 *Reagents and conditions*: (i) AcOH, reflux under inert atmosphere, 1 h.



Scheme 5 *Reagents and conditions:* (i) concd H_2SO_4 100 °C, 8 h, (ii) concd HCl, reflux, 8 h.

The application of 4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**14**) for the heterocyclization has recently been studied.[22] Aminopyrrole **8** reacts smoothly with **14** to afford compound **15**,[23] the product of initial attack of β-position of vinyl function on the amino moiety of the aminoheterocycle (Scheme 4). Reaction proceeds in absolute DMF by 85 °C under inert atmosphere.

This intermediate undergoes 6-*exo*-trig cyclization under the harsh conditions (melting at 180 °C) yielding 1-*tert*-butyl-4-(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3 carbonitrile (**16**).[24] For the α-substituted pyridines the coupling constant ($^3J_{HH}$) between α- and β-protons is expected to be about 8 Hz. In the case of **16** this coupling constant was measured to be 4.7 Hz, which strongly suggests the γ-CF_3 substitution of the formed pyridine.

Slow crystallization of compound **11c** from DMSO afforded stable diffraction-quality crystals. Single-crystal X-ray investigation confirmed the pyrrolopyridine structure of molecule **11c** unambiguously.[25]

Finally, pyrrolopyridines **11a** and **13** were transformed to the substrates **17** suitable for glycosylation possessing the free first position. This reaction was carried out in a two-step procedure. During the first step the *tert*-butyl-protected pyrrolopyridine carbonitrile was treated with concentrated sulfuric acid for a period of eight hours at 100 °C. Lower temperatures resulted quantitatively in the *tert*-butyl-protected carboxylic acid. The decarboxylation was carried out under reflux in concentrated hydrochloric acid. The compounds **17** were obtained in moderate yields (Scheme 5).

In summary, a convenient synthetic approach to the fluorinated pyrrolo[2,3-*b*]pyridine ring system was developed based on the commercially available 5-amino-1-*tert*-butyl-1*H*-pyrrole-3-carbonitrile (**8**) and the series of 1,3-CCC fluorine-containing biselectrophiles. The elaborated method gives rise to pyrrolo[2,3-*b*]pyridine bearing the polyfluoroalkyl substituent by the C-4 atom of the annulated pyridine ring. The reactions described demonstrate the practical use of the evaluated method, which also allows one to build up libraries of scaffolds **17**. The pyrrolopyridines of type **17** are considered as potent pharmacophor. The attempts to synthesize N-glycosylated and N-alkylated 4-(polyfluoroalkyl)-1*H*-pyrrolo[2,3-*b*]pyridines are currently under investigation in our laboratory.

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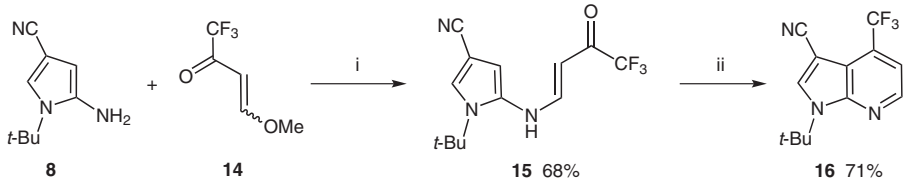

Scheme 4 *Reagents and conditions*: (i) in absolute DMF under inert atmosphere, 85 °C, 12 h; (ii) without solvent, under inert atmosphere 180 °C, 5 h.

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(20) **1-*tert*-Butyl-4-[chloro(difluoro)methyl]-6-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (11e)**
Colorless solid (0.65g, 90%); mp 234 °C (from EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.87 (9 H, s, CH_3), 7.53 (3 H, br m), 8.07 (1 H, s), 8.18 (2 H, d, $^3J_{CH}$ = 7.8 Hz), 8.70 (1 H, s). ^{13}C NMR (100.5 MHz, DMSO-d_6): δ = 28.9, 59.5, 81.9, 109.4 (t, $^3J_{CF}$ = 6.4 Hz), 112.8 (t, $^3J_{CF}$ = 2.4 Hz), 114.9, 124.6, (t, $^1J_{CF}$ = 290 Hz), 126.9, 129.0, 129.6, 135.2 (t, $^2J_{CF}$ = 30 Hz), 137.8, 139.7, 148.0, 151.3. MS: *m/z* (%) = 361(13) [M^+ + 2], 359(36) [M^+], 304(23), 303(100), 269(16), 268(75), 57(13). Anal. Calcd for $C_{19}H_{16}ClF_2N_3$: C, 63.42; H, 4.48; Cl, 9.85; F, 10.56; N, 11.68. Found: C, 63.50; H, 4.53; N, 11.75.

(21) **The General Procedure for Synthesis of Pyrrolo[2,3-*b*]pyridines 11 and 13**
5-Amino-1-*tert*-butyl-1*H*-pyrrole-3-carbonitrile (0.33 g, 2 mmol) and diketone **10** (or **12**, 2.2 mmol) were dissolved in AcOH (20 mL) and heated under reflux in the inert atmosphere during 1 h. Then this solution was evaporated under reduced pressure, treated with H_2O, filtrated, and dried on the air and recrystallized from an appropriate solvent, or was subjected to column chromatography over SiO_2.

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(23) **The Procedure for the Synthesis of (*E*)-1-*tert*-Butyl-5-(4,4,4-trifluoro-3-oxobut-1-enylamino)-1*H*-pyrrole-3-carbonitrile (15)**
5-Amino-1-*tert*-butyl-1*H*-pyrrole-3-carbonitrile (0.66 g, 4 mmol) and **14** (0.68 g, 4.4 mmol) were dissolved in abs. DMF (10 mL) and heated under inert atmosphere at 85 °C for 12 h. The solution was evaporated under reduced pressure, treated with H_2O, and dried under reduced pressure. Afterwards, the residue was subjected to column chromatography over SiO_2.
Colorless solid (0.78 g, 68%); mp 116–118 °C; R_f = 0.75 (hexane–EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): d = 1.59 (9 H, s, CH_3), 5.68 (1 H, d, $^3J_{HH}$ = 8 Hz), 6.20 (1 H, s.), 7.13 (1 H, s), 7.29 (1 H, dd, $^3J_{HH}$ = 8 Hz, $^3J_{HH}$ = 4 Hz), 11.80 (1 H, d, $^3J_{HH}$ = 4 Hz, NH). ^{13}C NMR (100.5 MHz, $CDCl_3$): d = 29.9, 58.1, 90.7, 91.0, 103.7, 119.8 (d, $^1J_{CF}$ = 285 Hz), 117.7, 131.0, 140.7, 153.3, 180.2 (q, $^2J_{CF}$ = 33 Hz). MS: *m/z* (%) = 286(11) [M^+ + 1], 285(56) [M^+], 239(22), 229(77), 170(11), 160(90), 57(100), 41(37). Anal. Calcd for $C_{13}H_{14}F_3N_3O$: C, 54.73; H, 4.95; F, 19.98; N, 14.73; O, 5.61. Found: C, 54.80; H, 4.98; N, 14.78.

(24) **Procedure for the Synthesis of 1-*tert*-Butyl-4-(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (16)**
1-*tert*-Butyl-5-(4,4,4-trifluoro-3-oxobut-1-enylamino)-1*H*-pyrrole-3-carbonitrile (**15**, 0.57 g, 2 mmol) in a 10 mL flask was melted for 5 h under inert atmosphere at 180 °C (temperature of the oil bath), then the dark-green residue formed was subjected to column chromatography over SiO_2.
Colorless solid (0.38 g, 71%); mp 161–163 °C. R_f = 0.75 (hexane–EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78

(9 H, s, CH_3), 7.41 (1 H, d, $^3J_{HH}$ = 4.7 Hz, H), 7.99 (1 H, s), 8.49 (1 H, d, $^3J_{HH}$ = 4.7 Hz). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 29.0, 59.3, 82.8, 113.8 (q, $^3J_{CF}$ = 4.7 Hz), 114.5, 115.7, 122.8 (q, $^2J_{CF}$ = 270 Hz), 129.8 (q, $^2J_{CF}$ = 35 Hz), 136.3, 143.7, 148.3. MS: *m/z* (%) = 267(48) [M^+], 212(58), 211(100), 192(24), 57(39), 56(10), 41(25). Anal. Calcd for $C_{13}H_{12}F_3N_3$: C, 58.42; H, 4.53; F, 21.33; N, 15.72. Found: C, 58.50; H, 4.59; N, 15.71.

(25) Crystallographic data (excluding structure factors) for the structure **11c** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 683574 and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; email: deposit@ccdc.cam.ac.uk, or via www.ccdc.cam.ac.uk/data_request/cif.