Facile Synthesis of Fluorinated 1-Desazapurines

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Dedicated to Professor Wolfgang Pfleiderer on the occasion of his 80th birthday

Abstract: A preparative approach towards 1-desazapurines, starting from 4(5)-aminoimidazoles and polyfluoroalkyl-containing 1,3-CCC-biselectrophiles was developed. As a result, a set of fluorinated 1-desazapurines was synthesized. Additionally, a synthetic route to 1-desazapurines bearing a sugar-mimicking group is proposed.

Key words: imidazoles, pyridines, annulations, fluorine, diketones, regioselectivity

Imidazo[4,5-b]pyridines (1-desazapurines) make up an important class of heterocyclic compounds that exhibit a wide range of biological activities and pharmacological properties.1 Purines and desazapurines possessing fluorine-containing substituents are rare in the literature, as there are no general synthetic approaches towards them. Fluorinated 1-desazapurines are potential phosphodiesterase inhibitors,2 GPR4 receptor antagonists,3a or inhibitors of aurora kinase.3b,c This indicates that fluorine-containing 1-desazapurines could be promising anticancer drugs.

Fluorinated purine4 nucleosides are attracting attention because of the high cytostatic activity of some 6-(trifluoromethyl)purine ribosides;4a adenosine A3 receptor antagonists4b indicate that the trifluoromethyl group facilitates hydration at the 6-position of the purine ring, and that the adducts forming at the 6-position might mimic the transition state of adenosine hydrolytic deamination.4c Nature synthesizes purine nucleotides by two general strategies: the first is a ‘de novo’ approach,5 via multistep nucleobase elaboration of 5-phospho-D-ribosylamine, and the second is a base ‘salvage’ strategy (Scheme 1).3a,b,6 The de novo synthetic pathway has unique linear solutions to the biosynthesis of various natural purines. However, the salvage pathway shares a common approach with the de novo one, namely the catalyzed addition of nucleobases to anomerically activated ribose. By modification of the known natural synthetic access, a potent pathway for assembling diverse fluorinated purine or 1-desazapurine nucleosides could be developed.

4(5)-Aminoimidazoles are potent starting materials for the synthesis of purines and 1-desazapurines, but data on the properties and synthetic potential of these amino-substituted heterocycles are very rare.8 During the course of pyridine and pyrimidine annulation studies involving cyclocondensation with aminoheterocycles,9 we have investigated the formation of fluorine-substituent-containing 1-desazapurines by the coupling of various fluorine-substituent-containing 1,3-CCC-biselectrophiles 4–10 (Figure 1) with 4(5)-aminoimidazoles.

Taking into account the low chemical stability of the commercially unavailable AIRs-riboside 17 (see Scheme 1), the de novo pathway to fluorinated purines and 1-desazapurines is precluded as a method for their assembly. However, the salvage nucleoside synthetic pathway has found broad application in the laboratory.

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current work (Scheme 2). One of these methods is based on the catalytic reduction of the corresponding nitro derivatives on palladium-on-carbon,\(^\text{10}\) and another proceeds via intermolecular interaction of amino and cyano groups.\(^\text{11}\) Yet another approach elaborated in our laboratory is based on the Curtius rearrangement, with subsequent hydrolysis of the formed isocyanates under acidic conditions. This novel procedure for the generation of 4(5)-aminoimidazoles in situ was successfully used by us for the generation of 2-aminobenzofuran.\(^\text{9b}\)

4-Nitroimidazoles 17 can be synthesized easily by two convenient methods, either by the basic alkylation of N-unsubstituted 4(5)-nitroimidazole,\(^\text{12}\) or by the reaction of 1,4-dinitro-1\(^H\)-imidazole 15 with aliphatic or aromatic amines 16 (Scheme 2).\(^\text{13}\) First, we investigated the interaction between aminoimidazole 11a (obtained by reduction) and diketones 4–7 (Scheme 3). Aminoimidazoles 11 appeared to be unstable in acetic acid media, and sensitive to oxygen; the destruction of the initial aminoheterocycles proceeds as fast as the corresponding cycloaddition, thereby reducing the overall yields.

To prevent the side reactions leading to aminoimidazole destruction, we used Schlenk techniques, and conducted the reactions under inert atmosphere in anhydrous solvents. It was found that the optimal conditions for the cyclization consisted of refluxing imidazoles 11 with fluorinated 1,3-diones 4–7 in dichloromethane under an argon atmosphere; this afforded imidazo[4,5-b]pyridines 23 as the sole products in 73–92% yields (Scheme 3, Table 1). The structures of the obtained fused pyridines 23 were confirmed by spectral criteria described by us previously.\(^\text{9b,f}\) Significant evidence for the \(\gamma\)-CF\(_3\) isomeric structure is provided by the chemical shifts of the CF\(_3\) group (\(^{19}\)F NMR: \(\delta = –62\)) and that of C7 (\(^{13}\)C NMR: \(\delta \approx 130, \quad \text{J}_{\text{CF}} \approx 30 \text{ Hz}\)).

**Figure 1** Variety of 1,3-CCC-biselectrophiles used for constructing imidazo[4,5-b]pyridines

**Scheme 2** Reagents and conditions: (i) DMF–AcOH, 140 °C.
Acylated δ-valerolactones 8 react with 11a depending on the reaction conditions (Scheme 3). Under neutral conditions in dichloromethane, the main product is compound 24; under acidic conditions, cycloaddition occurs and the reaction delivers the corresponding imidazo[4,5-b]pyridines 25.

The reactions of 1,3-diketones 9 and 10 with aminoimidazole 11 yield polycyclic imidazopyridines 26 and 27. The fused imidazopyridine 26 is an unknown heterocyclic system. In this case, methanol was used as solvent instead of dichloromethane, and p-toluenesulfonic acid was used as the acid catalyst (Scheme 3).

For the generation of aminimidazoles 22 in situ from acyl azides 20 by Curtius rearrangement, acetic acid provided the best reaction conditions (Scheme 2). However, aminimidazoles 22 are very unstable under these conditions, and decompose so fast that attempts to isolate pure compounds as the free base or salt failed. However, when the Curtius rearrangement is carried out in the presence of excess diones 4–7 and water, dezazapurines 28 form (Scheme 4). The most convenient procedure for the transformation appears to be slow addition of an N,N-dimethylformamide solution of azide 20 and building blocks 4–7 in a 1:3 ratio to a boiling acetic acid–water (25:1) mixture, followed by workup. In this case, compounds 28 formed in 73–93% yields. Side products 29 were seen in the 19F NMR spectra of the reaction mixture. The spectral data of compounds 28 thus obtained have similarities to those of compounds 23, thus confirming their structure. It should be noted that the methylsulfanyl group in 28b can be removed by treatment with freshly prepared Raney nickel in ethanol (Scheme 4, Table 2).

Aminoheterocycles 13 are less reactive, and, as a result, more stable. Thus, cyclization to form imidazo[4,5-b]pyridines 30 and 31 can be carried out in acetic acid. However, to optimize the yields, the reaction was performed in absolute ethanol under reflux for four to five hours in an inert atmosphere in the presence of a catalytic amount of p-toluenesulfonic acid. According to GC-MS and 19F NMR spectroscopy, the reactions proceeded regioselectively, producing only the γ-CF₃ isomers in 79–89% yields (Scheme 5, Table 3). The most convincing evidence for the formation of structures 30 is the presence of long-range coupling (J_HF ~ 2 Hz, J_CF ~ 5 Hz) between the methyl group in the 1-position and the fluorine of the trifluoromethyl group on the 7-position of the ring.

The use of 4-aminimidazoles 12 was also attempted (Scheme 6). This isomer is unstable and earlier was used only in situ as a 1,4-dioxane solution after reduction of the corresponding nitro derivatives. We found that the fast evaporation of 1,4-dioxane in vacuo without heating allowed us to obtain compounds 12 in pure form. Imidazoles 12 should be used immediately for further reactions.

### Table 1: Yields of Imidazo[4,5-b]pyridines 23

<table>
<thead>
<tr>
<th></th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
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<th>Yield (%)</th>
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<tr>
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<td>Me</td>
<td>CF₃</td>
<td>CF₃</td>
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<tr>
<td>23b</td>
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<td>Me</td>
<td>Ph</td>
<td>CF₃</td>
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<tr>
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### Table 2: Yields of Imidazo[4,5-b]pyridines 28

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</table>

* Yield of 28e from 28c.

### Scheme 4: Reagents and conditions

(i) DMF–AcOH, 140 °C; (ii) Raney Ni, EtOH, 2 h.

### Scheme 5: Reagents and conditions

(i) MeOH, PTSA, reflux, 2–3 h.

### Scheme 6: Reagents and conditions

(i) MeOH, PTSA, reflux, 2–3 h.
transformations. Thus the reactions of 12 with diones 4 and 5 in ethanol in the presence of $p$-toluenesulfonic acid afford the corresponding imidazo[4,5-b]pyridines 32 in 43–70% yields. Acetic acid can also be used as solvent in the reaction, but then more side product forms. NMR spectra of these compounds have spectral patterns similar to those of compound 23 and 28. In this case, the presence of long-range coupling (e.g., $J_{CF} \approx 5$ Hz for 32e,f) between the groups in the 1-position and the trifluoromethyl group is evidence for $\gamma$-CF$_3$ isomer formation (Scheme 6, Table 4).

The benzyl group was specially introduced into 32c as a protecting group (Scheme 6) at the 4-nitroimidazole stage, with the purpose of subsequent cleavage at the 1-desazapurines stage. The protecting group was removed by hydrogenation over palladium on carbon in PARR apparatus. The substitution pattern in 5,7-bis(trifluoromethyl)-3H-imidazo[4,5-b]pyridine (33) is convenient for subsequent glycosylation with the purpose to synthesize the corresponding fluorinated 1-desazapurine nucleosides and nucleoside mimetics (Scheme 6).

To demonstrate the suitability of 1-desazapurines for nucleoside synthesis, we studied the reaction of 33 with the acyclic sugar mimetic 2-(bromomethoxy)propane-1,3-diyldibenzoate (34),$^{14}$ compound 37,$^{15}$ and (4-acetoxy-clopent-2-enyl)methyl acetate (40),$^{16}$ with the purpose to develop a preparative synthetic pathway towards 1-desazapurine carbanucleosides and nucleoside mimetics (Scheme 7).

The alkylation of 33 with 34 was performed by the generally described method$^{17}$ for nitropyrole alkylation; it was conducted with sodium hydride in anhydrous acetonitrile to produce the precursor ester derivatives 35. Deprotection of the sugar mimetic group was carried out by treatment of 35 with a solution of ammonia in methanol (Scheme 7).$^{17}$ Compound 36 can be considered as an analogue of ganciclovir,$^{18}$ a potent HBV inhibitor, both in cell culture against duck-HBV (DHBV) and in animal models. The building blocks 37 and 40 were recently used for the synthesis of the two well-known biologically active molecules aristeromycin$^{19}$ and carbovir,$^{20}$ respectively. Subjecting 37 to a Mitsunobu reaction, according to a previously described method,$^{15}$ with 1-desazapurines 33, followed by a two-step, one-pot sequence consisting of

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### Table 3 Yields of Imidazo[4,5-b]pyridines 30

<table>
<thead>
<tr>
<th>30</th>
<th>R$^1$</th>
<th>R$^2$</th>
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<td>CF$_3$</td>
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<td>CF$_3$</td>
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<tr>
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<td>Ph</td>
<td>Me</td>
<td>C$_2$F$_3$</td>
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</table>

### Table 4 Yields of Imidazo[4,5-b]pyridines 32

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<th>R$^1$</th>
<th>R$^2$</th>
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<td>32b</td>
<td>Ph</td>
<td>2-thienyl</td>
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<tr>
<td>32c</td>
<td>Bn</td>
<td>CF$_3$</td>
<td>69</td>
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<td>Bn</td>
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<td>51</td>
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<tr>
<td>32e</td>
<td>(S)-1-phenylethyl</td>
<td>CF$_3$</td>
<td>49</td>
</tr>
<tr>
<td>32f</td>
<td>(R)-1-phenylethyl</td>
<td>CF$_3$</td>
<td>43</td>
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oxidative cleavage of the double bond with osmium tetroxide/sodium periodate, followed by sodium borohydride reduction provided 38 in 57% yield (Scheme 7). The deprotection of 38 was carried out in a trifluoroacetic acid–water mixture (9:1).9b Stereoselective palladium-catalyzed alklylation10 of 33 by 40 gave 41. The reaction proceeds smoothly, leading to the formation of only the cis-isomer of 41 in a 51% yield (Scheme 7).

The formation of the 9-isomer was confirmed by 1H, 13C, and 19F NMR spectroscopy. Additionally, the through-space coupling between the carbon nuclei in the 9-position and the CF3 group in the 6-position typical for the 7-isomers was not observed for 36, 39, and 41 (Scheme 7). The main evidence for the presence of a sugar-mimicking group in the 9-position of the 1-desazapurine framework was provided by 2D NMR spectral correlation. The HMBC spectra of compound 35 show a long-range interaction between carbon C-7a at δ = 161 in the 1-desazapurine skeleton with the protons at δ = 6.01 of the OCH2 fragment of the (methoxy)propane-1,3-diy1 moiety (Figure 2). In compound 38, carbon C-7a correlated in the HMBC spectrum with the anomeric proton at δ = 4.85–4.91 in position 6 of the cyclopentane-1,2,3-triol group (Figure 2).

![Figure 2 Significant NMR data of compounds 35 and 38](image)

In summary, reactions of 4(5)-aminoimidazoles 11, 12, 13, and 22 with fluorine-substituent-containing 1,3-CCC-biselectrophiles 4–10 were investigated. A convenient synthetic approach towards 1-desazapurines substituted at the 6-position by fluorine-containing groups was elaborated. The simple synthetic procedures and satisfying yields make these methods promising and very attractive for the synthesis of various substituted 1-desazapurines, useful scaffolds for organic and medicinal chemistry. Experiments to study the glycosylation reactions of 3H-imidazo[4,5-b]pyridines, obtained in much the same way as 33, with the purpose to obtain corresponding nucleosides, desoxynucleosides, and their mimetics, are currently under way in our laboratory.

All solvents were purified and dried by standard methods. NMR spectra were recorded on Jeol JNM-LA 400, Varian VXR-300, Varian Mercury-400, and Bruker 600 spectrometers. TMS was used as an internal standard for 1H and 13C NMR spectroscopy, and CFCl3 was used for 19F NMR spectroscopy. IR spectra were recorded on a Perkin Elmer FTIR 1600 spectrometer for samples prepared as KBr discs. Mass spectra were obtained on a Hewlett-Packard HPGC/MS 5890/5972 instrument (EI, 70 eV) for which a GC inlet was used, or on a MX-1321 instrument (EI, 70 eV) with a direct inlet. Column chromatography was performed on silica gel (63–200 mesh, Merck). Silica gel plates (Merck 60F254) were used for TLC. 1-Substituted 4-nitro-1H-imidazoles 17 were obtained,15 and 4(5)-nitroimidazoles were reduced12 according to published procedures. Fluorinated 1,3-dicarbonyl compounds were obtained by Claisen-type condensation of the appropriate carbonyl compounds with the corresponding fluorinated acid esters in the presence of NaOMe or LiH.21 The corresponding imidazole-5-carbonyl chloride used for the preparation of acyl azides 20 was obtained from the corresponding acids.22 Compounds 35,14 38,15 and 4116 were prepared according to published procedures.

4(5)-Aminimidazoles 11, 12, and 13; General Procedure

The appropriate nitroimidazole (0.1 mol) and 10% Pd/C (2 g) were placed in a 2-L, one-necked round-bottomed Schlenk flask under a flow of anhyd argon. Anhyd, degassed 1,4-dioxane (1300 mL) was added. The hydrogenation was conducted with the aid of a big glass burette under atmospheric pressure. After the H2 (3 equiv) had been absorbed (ca. 12–16 h), the reaction mixture was filtered through a Kieselgur pad (3–5 cm thick). The kieselguhr was washed a few times with 1,4-dioxane. The solvent was removed under reduced pressure (the temperature of the water bath should not rise above 40 °C) and the residue was dried under reduced pressure over 2 d. The thus formed aminoimidazoles (11a, dark yellow residue; 11b, 13, orange oils) are not stable and extremely sensitive to heat and O2. However, they could be stored in a sealed flask under an argon atmosphere at −25 °C for at least 1 month. With time, the material becomes darker. All subsequent manipulations with these compounds were conducted under an inert atmosphere; the starting material was transferred in a glovebox in an anhyd and inert atmosphere. Reactions were carried out in anhyd solvents, since the commercially available aminoimidazoles have been described to be hydrolytically unstable.

1,2-Dimethyl-1H-imidazol-5-amine (11a)

Yellow solid.

1H NMR (CDCl3): δ = 2.21 (s, CH3), 3.3 (s, NCH3), 4.51 (br s, NH2), 6.21 (s, CH).

2-(5-Amino-2-methyl-1H-imidazol-1-yl)ethanol (11b)

Orange oil.

1H NMR (CDCl3): δ = 2.25 (s, 3 H, CH3), 3.58 (t, JHH = 7.4 Hz, 2 H, CH2), 3.71 (t, JHH = 7.4 Hz, 2 H, CH2), 4.51 (br s, 2 H, NH), 6.23 (s, 1 H, CH).

1-[(S)-1-Phenylethyl]-1H-imidazol-4-amine (12a)

Orange oil.

1H NMR (CDCl3): δ = 1.69 (d, JHH = 6.8 Hz, 3 H, CH3), 4.73 (br s, 2 H, NH2), 5.09 (q, JHH = 6.8 Hz, 1 H, CH), 6.40 (br s, 1 H, CH), 7.25 (br s, 1 H, CH), 7.33 (br m, 2 H, CH), 7.41 (br m, 3 H, CH).

1-[(R)-1-Phenylethyl]-1H-imidazol-4-amine (12b)

Orange oil.

1H NMR (CDCl3): δ = 1.64 (d, JHH = 6.8 Hz, 3 H, CH3), 4.73 (br s, 2 H, NH2), 5.03 (q, JHH = 6.8 Hz, 1 H, CH), 6.40 (br s, 1 H, CH), 7.25 (br s, 1 H, CH), 7.35 (br m, 2 H, CH), 7.40 (br m, 3 H, CH).

1-Phenyl-1H-imidazol-4-amine (12d)

Orange oil.

1H NMR (CDCl3): δ = 5.01 (br s, 2 H, NH2), 6.59 (br s, 1 H, CH), 7.30 (br m, 3 H, CH), 7.43 (br m, 2 H, CH), 7.55 (br s, 1 H, CH).
1-Benzyl-1H-imidazol-4-amine (12e)
Orange oil.

\[ \text{H NMR (CDCl}_3\text{): } \delta = 4.73 \text{ (s, 2 H, NH)}_2\text{), 4.81 (s, 2 H, CH)}_2. \]

Yellow oil; yield: 4.52 g (52%); \( R_f = 0.75 \) (EtOAc).

\[ \text{H NMR (CDCl}_3\text{): } \delta = 4.87 \text{ (s, 2 H, } \text{NCH}_2\text{)}, 5.26 \text{ (s, 2 H, CH)}_2. \]

Yellow oil; yield: 4.52 g (52%); \( 139.0, 142.3 \).

\[ \text{H NMR (CDCl}_3\text{): } \delta = 4.87 \text{ (s, 2 H, } \text{NCH}_2\text{)}, 5.26 \text{ (s, 2 H, CH)}_2. \]

Pale yellow solid; yield: 1.81 g (85%); \( 139.0, 142.3 \).

3-Phenyl-1H-imidazole-4-carbonyl Azide (20b)
Pale yellow solid; yield: 1.81 g (85%); \( R_f = 0.75 \) (EtOAc).

**Imidazo[4,5-b]pyridines 23 and 24 from 5-Aminimidazole 11 and Fluorine-Containing 1,3-Diketones; General Procedure**
A mixture of the appropriate aminimidazole 11 (2 mmol) and diketone (2.2 mmol) was heated under reflux in CHCl\(_3\) (25 mL) in an inert atmosphere for 6–10 h. Afterwards the solvent was evaporated under reduced pressure, and the crude material that had formed was recrystallized from an appropriate solvent, or subjected to column chromatography (silica gel).

2,3-Dimethyl-5,7-bis(trifluoromethyl)-1H-imidazo[4,5-b]pyridine (23a)

**Colorless solid; yield: 0.5 g (89%);** mp 57–59 \( ^\circ \text{C} \).

\[ \text{H NMR (CDCl}_3\text{): } \delta = 2.67 \text{ (s, 3 H, } \text{CH})_3\text{), 3.84 (s, 3 H, CH)}_3. \]

**MS (EI, 70 eV):** 121.2, 121.7, 123.3, 126.9, 136.2, 137.4, 146.8.

3-[4-(Nitro-1H-imidazol-1-yl)ethyl]-1H-indole (23c)

\[ \text{H NMR (CDCl}_3\text{): } \delta = 7.16 \text{ (t, } \text{J} = 4.2 \text{ Hz, 1 H, CH}), 7.66 \text{ (d, } \text{J} = 4.2 \text{ Hz, 1 H, CH), 7.95–8.00 (br m, 2 H, } \text{CH}) \).

**MS (EI, 70 eV):** \( m/z \) = 292 [M\(^+\) + 1] (20), 291 [M\(^+\)] (100), 280 (19), 268 (24), 264 (15), 262 (11), 215 (20), 195 (18).

7-(Chlorodifluoromethyl)-2,3-dimethyl-5-phenyl-3H-imidazo[4,5-b]pyridine (23d)

**Colorless solid; yield: 0.54 g (92%);** mp 179–180 \( ^\circ \text{C} \) (EtOH).

\[ \text{H NMR (CDCl}_3\text{): } \delta = 6.33 \text{ (d, } \text{J} = 8.4 \text{ Hz, 1 H, CH}), 7.29 \text{ (t, } \text{J} = 4.2 \text{ Hz, 1 H, CH), 7.62 (d, } \text{J} = 4.2 \text{ Hz, 1 H, CH), 7.95–8.00 (br m, 2 H, CH) \).

**MS (EI, 70 eV):** \( m/z \) = 284 [M\(^+\) + 1] (12), 283 [M\(^+\)] (100), 282 (19), 268 (24), 264 (15), 262 (11), 215 (20), 195 (18).

Acyl Azides 20a,b; General Procedure
The appropriate imidazol-5-carboxylic chloride (10 mmol) was dissolved in anhyd DMF (20 mL) and added dropwise to a suspension of NaN\(_3\) (1.3 g, 20 mmol) in anhyd DMF (10 mL). After addition was completed, the mixture was left overnight, and poured into H\(_2\)O (2×), and dried under reduced pressure. These two azides 20a,b are stable and can be stored for a long time in the refrigerator at \(-20^\circ \text{C}\).

2-(Methylsulfanyl)-3-phenyl-3H-imidazole-4-carbonyl Azide (20a)
Pale yellow solid; yield: 2.33 g (90%); mp 207 \( ^\circ \text{C} \) (dec.).

\[ \text{H NMR (CDCl}_3\text{): } \delta = 2.56 \text{ (s, 3 H, CH)}_3. \]

7-(Chlorodifluoromethyl)-2,3-dimethyl-5-phenyl-3H-imidazo[4,5-b]pyridine (23d)

**Colorless solid; yield: 0.52 g (73%);** mp 168–170 \( ^\circ \text{C} \) (i-PrOH).

\[ \text{H NMR (CDCl}_3\text{): } \delta = 7.29 \text{ (d, } \text{J} = 8.4 \text{ Hz, 1 H, CH}), 7.35 \text{ (t, } \text{J} = 73.8 \text{ Hz, 1 H, CH), 8.02 (s, 1 H, CH), 8.28 (d, } \text{J} = 8.4 \text{ Hz, 1 H, CH) \).

**MS (EI, 70 eV):** \( m/z \) = 357 [M\(^+\) + 1] (19), 357 [M\(^+\)] (100), 307 (27), 306 (17), 278 (10).

7-(Chlorodifluoromethyl)-2,3-dimethyl-5-phenyl-3H-imidazo[4,5-b]pyridine (23d)

**Colorless solid; yield: 0.52 g (84%);** mp 135–138 \( ^\circ \text{C} \) (i-PrOH).

\[ \text{H NMR (CDCl}_3\text{): } \delta = 7.75 \text{ (s, 3 H, CH)}_3. \]

Orange oil.
2-[2-Methyl-5-phenyl-7-(trifluoromethyl)-3H-imidazo[4,5-b]pyridin-3-yl]ethanol (23c)

Colorless solid; yield: 0.56 g (87%); mp 158–159 °C; Rf = 0.40 (EtOAc–hexane, 1:2).

1H NMR (CDCl3): δ = 2.67 (s, 3 H, 2-CH3), 3.71 (br s, 1 H, CH), 4.06 (t, JCH = 4.8 Hz, 2 H, CH2), 4.40 (t, JCH = 4.8 Hz, 2 H, CH2), 7.35–7.45 (br m, 3 H, CH), 7.77 (s, 1 H, CH), 7.94 (d, JCH = 8.2 Hz, 2 H, CH2).

13C NMR (CDCl3): δ = 14.3, 45.9, 60.7, 111.0 (q, JCF = 4 Hz), 122.5 (q, JCF = 275 Hz), 126.4, 126.7, 127.1 (q, JCF = 33 Hz), 128.3, 128.6, 129.3 (q, JCF = 1.6 Hz), 137.7, 149.1, 150.9, 155.8.

19F NMR (CDCl3): δ = –62.1.

MS (EI, 70 eV); m/z (%): 322 [M+ + 1] (10), 321 [M+] (100), 291 (33), 271 (43), 266 (18), 247 (12), 278 (18), 277 (100), 276 (33), 270 (13).

3-[1-(5-Amino-1,2-dimethyl-1H-imidazol-4-yl)-2,2,3,3,3-pentafluoro-1-hydroxypropyl]tetrahydro-2H-pyran-2-one (24)

Colorless solid; yield: 0.34 g (48%); mp 95–97 °C; Rf = 0.45 (EtOAc).

1H NMR (DMSO-d6): δ = 1.61–1.70 (m, 4 H, CH), 2.65 (s, 3 H, 2-CH3), 3.35 (m, 1 H, CH), 3.82 (s, 3 H, 1-CH3), 4.18 (m, 2 H, CH), 6.25 (br m, 3 H, NH2+OH).

13C NMR (DMSO-d6): δ = 13.5, 22.3, 24.4, 28.1, 43.2, 68.3, 72.1 (t, JCH = 14.7, 28.2, 29.4, 31.0, 59.9, 123.1 (q, JCF = 275 Hz), 130.1, 139.3, 141.0, 154.0, 165.8.

MS (EI, 70 eV): m/z (%): 357 [M+] (31), 351 (19), 341 (29), 327 (53), 258 (15), 257 (100), 239 (25), 96 (70).

1-Desazapurines 25, 26, 28, 30, and 31; General Procedure

A mixture of the appropriate aminoimidazole (2 mmol) and diketone (2.2 mmol) in absolute MeOH (20 mL) with a catalytic amount of PTSA was heated under reflux under an inert atmosphere for 2–3 h. The solvent was evaporated under reduced pressure. The material that had formed was recrystallized from an appropriate solvent, or was subjected to column chromatography (silica gel).

6-(3-Hydroxypropyl)-2,3-dimethyl-7-(trifluoromethyl)-3,4-dihydro-5H-imidazo[4,5-b]pyridin-5-one (25a)

Colorless solid; yield: 0.35 g (61%); mp 157–158 °C (i-PrOH).

1H NMR (DMSO-d6): δ = 1.69 (br m, 2 H, CH), 2.69 (s, 3 H, 2-CH3), 2.85 (t, 2 H, JCH = 5.6 Hz), 3.78 (s, 3 H, 1-CH3), 4.07 (t, 2 H, JCH = 6.4 Hz), 4.38 (br s, 1 H, OH), 12.04 (br s, 1 H, NH).

13C NMR (DMSO-d6): δ = 14.7, 28.2, 29.4, 31.0, 59.9, 123.1 (q, JCF = 275 Hz), 132.0 (q, JCF = 33 Hz), 130.1, 139.3, 141.0, 154.0, 165.8.

MS (EI, 70 eV): m/z (%): 290 [M+ + 1] (11), 289 [M+] (11), 271 (17), 266 (18), 178 (100), 43 (35).

6-(3-Hydroxypropyl)-2,3-dimethyl-7-(pentafluoroethyl)-3,4-dihydro-5H-imidazo[4,5-b]pyridin-5-one (25b)

Colorless solid; yield: 0.36 g (67%); mp 74–75 °C; Rf = 0.85 (EtOAc–hexane, 1:3).

1H NMR (CDCl3): δ = 1.75–1.84 (br m, 4 H, CH), 2.56 (s, 3 H, 2-CH3), 2.94–2.99 (br m, 4 H, CH), 3.68 (s, 3 H, CH3).

13C NMR (CDCl3): δ = 14.1, 22.3, 22.5, 25.7 (q, JCF = 3.2 Hz), 28.3, 33.4, 123.4 (q, JCF = 275 Hz), 124.6 (q, JCF = 2.4 Hz), 124.9 (q, JCF = 32 Hz), 129 (q, JCF = 1.6 Hz), 147.2, 152.4, 154.6, 174.3.

MS (EI, 70 eV): m/z (%): 269 [M+] (100), 240 (17), 202 (33), 161 (14), 124 (21), 67 (15).

1-Desazapurines 28 from Azides 20; General Procedure

A mixture of the appropriate dielectrophile (1 mmol) and azide (3 mmol) in anhyd DMF (40 mL) was added dropwise, very slowly, through the long condenser above a boiling soln of AcOH (30 mL) and H2O (2 mL) (oil bath temperature ca. 145 °C). After complete addition, the mixture was refluxed for another 3 h. After evaporation of the solvent, the residue was subjected to column chromatography (silica gel), or recrystallized from an appropriate solvent. A 1:3 azide/electrophirole ratio is recommended for providing an almost quantitative yield of the 1-desazapurines.

2-(Methylsulfanyl)-3-phenyl-5,7-bis(trifluoromethyl)-3H-imidazo[4,5-b]pyridine (28a)

Colorless solid; yield: 0.33 g (88%); mp 157–159 °C (i-PrOH).

1H NMR (CDCl3): δ = 0.75 (s, 3 H, 2-CH3), 7.43–7.55 (br m, 5 H, CH), 7.71 (s, 1 H, CH).

13C NMR (CDCl3): δ = 14.4, 24.3, 111.4 (m), 122.3 (q, JCF = 275 Hz), 123.2 (q, JCF = 275 Hz), 125.8 (q, JCF = 33 Hz), 127.1, 129.9, 132.7, 134.3, 140.5 (q, JCF = 33 Hz), 151.1, 162.6.

MS (EI, 70 eV): m/z (%): 378 [M+ + 1] (15), 377 [M+] (81), 362 (11), 344 (13), 342 (19), 268 (13), 92 (13), 91 (100), 77 (25), 51 (12).

5-Methyl-2-(methylsulfanyl)-3-phenyl-7-(trifluoromethyl)-3H-imidazo[4,5-b]pyridine (28b)

Colorless solid; yield: 0.30 g (93%); mp 145–147 °C (i-PrOH).

1H NMR (CDCl3): δ = 2.51 (s, 3 H, 5-CH), 2.68 (s, 3 H, 2-CH3), 7.15 (s, 1 H, CH), 7.37–7.49 (br m, 5 H, CH).
\[^{13}\text{C} \text{NMR (CDCl}_3\):} \delta = 14.2, 24.3, 113.7 (q, \Delta_{\text{CF}} = 4.6 \text{ Hz}), 122.3 (q, \Delta_{\text{CF}} = 275 \text{ Hz}), 126.0 (q, \Delta_{\text{CF}} = 33 \text{ Hz}), 127.3, 129.3, 129.6, 129.9 (q, \Delta_{\text{CF}} = 1.6 \text{ Hz}), 133.5, 150.9, 152.2, 157.2.

\[^{19}\text{F} \text{ NMR (CDCl}_3\):} \delta = -61.7.

MS (EL, 70 eV): m/z (%) = 324 [M* + 1] (20), 323 [M*] (100), 308 (22), 290 (25), 214 (35), 91 (42), 77 (11).

2-(Methylsulfonyl)-3,5-diphenyl-7-(trifluoromethyl)-1,3,5-imidazo[4,5-b]pyridine (28c)

Colorless solid; yield: 0.27 g (87%); mp 150–152 °C (EtOH).

MS (EI, 70 eV): m/z (%) = 306 [M+ + 1] (20), 305 [M+] (100), 304 (19), 187 (16), 145 (11), 144 (11), 126 (10), 91 (28), 77 (23).

3-Phenyl-7-(trifluoromethyl)-1,3,5-imidazo[4,5-b]pyridine (28d)

Colorless solid; yield: 0.34 g (89%); mp 153–155 °C (EtOH).

MS (EI, 70 eV): m/z (%) = 320 [M+ + 1] (20), 319 [M+] (100), 308 (23), 190 (10), 189 (10), 188 (10), 187 (9), 174 (10), 166 (10), 151 (10), 139 (10), 127 (10), 126 (10), 115 (10), 114 (10), 93 (10), 92 (10), 77 (10), 65 (10), 64 (10), 53 (10), 39 (10), 38 (10), 37 (10).

3-Phenyl-5-(2-thienyl)-7-(trifluoromethyl)-1,3,5-imidazo[4,5-b]pyridine (28e)

Colorless solid; yield: 0.66 g (87%); mp 193–194 °C (i-PrOH).

MS (EI, 70 eV): m/z (%) = 363 [M+ + 2] (39), 362 [M+ + 1] (21), 355 [M*] (100), 321 (20), 320 (88), 77 (23).

1,3,5-Trimethyl-7-(trifluoromethyl)-1,3,5-dihydro-2H-imidazo[4,5-b]pyridine-2-thione (30a)

Colorless solid; yield: 0.44 g (84%); mp 59–61 °C; Rf = 0.30 (EtOAc–hexane, 1:4).

MS (EI, 70 eV): m/z (%) = 262 [M+ + 1] (16), 362 [M* + 1] (21), 361 [M*] (100), 326 (64), 77 (17).

1,3,5-Trimethyl-7-(trifluoromethyl)-1,3,5-dihydro-2H-imidazo[4,5-b]pyridine-2-thione (30b)

Colorless solid; yield: 0.58 g (89%); mp 223–226 °C (i-PrOH).

MS (EI, 70 eV): m/z (%) = 262 [M+ + 1] (16), 362 [M* + 1] (21), 361 [M*] (100), 326 (64), 77 (17).

1-Methyl-3-phenyl-5,7-bis(trifluoromethyl)-1,3,5-dihydro-2H-imidazo[4,5-b]pyridine-2-thione (30c)

Colorless solid; yield: 0.66 g (87%); mp 193–194 °C (i-PrOH).
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1H NMR (CDCl3): δ = 2.37 (s, 3 H, CH3), 7.05 (t, \( J_{HH} \) = 4.2 Hz, 1 H, CH), 7.31–7.36 (br m, 3 H, CH), 7.45–7.51 (br m, 3 H, CH), 7.64 (d, \( J_{HH} \) = 4.2 Hz, 2 H, CH), 7.76 (s, 1 H, CH), 8.19 (s, 1 H, CH).

13C NMR (DMSO-d6): δ = 111.5 (t, \( J_{CF} \) = 5.6 Hz), 118.4, 122.3 (q, \( J_{CF} \) = 275 Hz), 122.4 (q, \( J_{CF} \) = 35 Hz), 126.8, 127.6 (q, \( J_{CF} \) = 1.6 Hz), 128.5, 128.9, 129.3, 129.6, 130.3, 136.4, 141.1, 148.2, 150.5, 158.0.

MS (EI, 70 eV): m/z (%) = 346 [M + 1] (20), 345 [M] (100), 77 (19).

1-Benzyl-5,7-bis(trifluoromethyl)-1H-imidazo[4,5-b]pyridine (32c)

Colorless solid; yield = 0.48 g (69%); mp 113–115 °C (i-PrOH).

1H NMR (DMSO-d6): δ = 5.76 (s, 2 H, CH), 7.10 (d, \( J_{HH} \) = 7.8 Hz, 2 H, CH), 7.36 (br m, 2 H, CH), 8.15 (s, 1 H, CH), 9.16 (s, 1 H, CH).

13C NMR (DMSO-d6): δ = 50.1 (q, \( J_{CF} \) = 4 Hz), 111.9, 121.4 (q, \( J_{CF} \) = 275 Hz), 121.5 (q, \( J_{CF} \) = 35 Hz), 121.7 (q, \( J_{CF} \) = 275 Hz), 123.7, 125.9, 127.7, 128.7, 135.9, 140.8, 153.6, 157.9.

MS (EI, 70 eV): m/z (%) = 346 [M + 1] (15), 345 [M] (67), 92(17), 91 (100), 65 (23).

1-Benzyl-7-(trifluoromethyl)-1H-imidazo[4,5-b]pyridin-5(4H)-one (32d)

Colorless solid; yield = 0.30 g (51%); mp 185–187 °C (i-PrOH).

1H NMR (DMSO-d6): δ = 5.50 (s, 2 H, CH), 6.72 (s, 1 H, CH), 6.93 (m, 2 H, CH), 7.29 (s, 3 H, CH), 8.42 (s, 1 H, CH), 12.02 (s, 1 H, NH).

13C NMR (DMSO-d6): δ = 102.2 (q, \( J_{CF} \) = 4.8 Hz), 122.7 (q, \( J_{CF} \) = 275 Hz), 124.1, 125.1 (q, \( J_{CF} \) = 1.6 Hz), 128.0, 129.5, 130.4 (q, \( J_{CF} \) = 33 Hz), 134.7, 143.0, 145.8, 161.0.

MS (EI, 70 eV): m/z (%) = 280 [M + 1] (11), 279 [M] (71), 104 (92), 93 (15), 78 (13), 77 (100), 69 (27), 51 (46), 43 (32).

1-([S]-1-Phenyl-1H)-7,5-bis(trifluoromethyl)-1H-imidazo[4,5-b]pyridine (32e)

Colorless solid; yield = 0.35 g (49%); mp 99–101 °C (EtOAc–hexane, 1:1).

1H NMR (CDCl3): δ = 1.88 (d, \( J_{HH} \) = 7.0 Hz, 3 H, CH3), 5.44 (m, 1 H, CH), 8.18 (s, 1 H, CH), 9.17 (s, 1 H, CH).

13C NMR (CDCl3): δ = 21.7, 59.9 (q, \( J_{CF} \) = 4.7 Hz), 111.5, 121.2 (q, \( J_{CF} \) = 275 Hz), 121.4 (q, \( J_{CF} \) = 35 Hz), 121.9 (q, \( J_{CF} \) = 275 Hz), 124.8, 126.3, 129.5, 129.8, 135.1, 140.1, 153.0, 158.1.

MS (EI, 70 eV): m/z (%) = 359 [M] (12), 105 (100), 77(10).

1-([R]-1-Phenyl-1H)-7,5-bis(trifluoromethyl)-1H-imidazo[4,5-b]pyridine (32f)

Colorless solid; yield = 0.31 g (43%); mp 100–101 °C; \( R \) = 0.75 (EtOAc–hexane, 1:1).

1H NMR (CDCl3): δ = 1.89 (d, \( J_{HH} \) = 7.0 Hz, 3 H, CH3), 5.44 (m, 1 H, CH), 8.17 (s, 1 H, CH), 9.18 (s, 1 H, CH).

13C NMR (CDCl3): δ = 21.7, 60.1 (q, \( J_{CF} \) = 4.6 Hz), 111.7, 121.2 (q, \( J_{CF} \) = 275 Hz), 121.4 (q, \( J_{CF} \) = 35 Hz), 122.0 (q, \( J_{CF} \) = 275 Hz), 124.8, 126.3, 129.5, 129.8, 135.1, 140.0, 153.1, 158.0.

MS (EI, 70 eV): m/z (%) = 359 [M] (13), 105 (100), 77 (12).

5,7-Bis(trifluoromethyl)-1H-imidazo[4,5-b]pyridine (33)

A mixture of 32c (0.56 g, 2 mmol) in absolute MeOH (20 mL) and 0.1 g of 10% Pd/C was intensively shaken in a PARR apparatus vessel under H₂ (5 atm) for 2 h. Then the precipitate was collected by filtration and washed several times with hot MeOH. The solvent was evaporated and the white residue was recrystallized from a small amount of MeOH.

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Colorless solid; yield: 0.28 g (54%); mp 279–280 °C (i-PrOH).

1H NMR (DMSO-d$_6$): $\delta$ = 7.11 (s, 1 H, CH), 7.11 (s, 1 H, CH), 12.07 (s, 1 H, NH).

13C NMR (DMSO-d$_6$): $\delta$ = 115.3, 122.7 (q, $^1$J$_{CF}$ = 275 Hz), 122.9 (q, $^1$J$_{CF}$ = 275 Hz), 127.7 (q, $^1$J$_{CF}$ = 35 Hz), 133.9, 141.4 (q, $^1$J$_{CF}$ = 35 Hz), 149.5, 161.4.

MS (EI, 70 eV): m/z (%) = 255 [M$^+$] (100), 254 (21).

2-[[5,7-Bis(trifluoromethyl)-3H-imidazol-4,5-b]-pyridin-3-yl)methoxy]propane-1,3-diol (35)

Compound 35 was prepared according to a published procedure.$^{14}$

Yellow oil; yield: 0.65 g (57%); R$_f$ = 0.90 (EtOAc–hexane, 1:3).

1H NMR (DMSO-d$_6$): $\delta$ = 4.33 (m, 4 H), 4.81 (br s, 2 H, CH$_2$), 6.01 (br s, 2 H, CH$_2$), 7.35 (br m, 6 H, CH), 7.77 (s, 1 H, CH), 7.87 (d, $^3$J$_{HH}$ = 7.2 Hz, 4 H), 8.37 (s, 1 H, CH).

13C NMR (DMSO-d$_6$): $\delta$ = 62.9, 69.7, 76.7, 115.4, 122.1 (q, $^1$J$_{CF}$ = 275 Hz), 122.7 (q, $^1$J$_{CF}$ = 275 Hz), 127.5 (q, $^1$J$_{CF}$ = 35 Hz), 128.8, 129.7, 130.5, 133.3, 133.9, 141.4 (q, $^1$J$_{CF}$ = 35 Hz), 149.1, 161.7, 188.9.

MS (EI, 70 eV): m/z (%) = 567 [M$^+$] (47), 445 (19), 313 (37), 283 (33), 282 (17), 161 (27), 105 (100), 77 (19), 67 (11).

2-[[5,7-Bis(trifluoromethyl)-3H-imidazol-4,5-b]-pyridin-3-yl)methoxy]propane-1,3-diol (36)

To a solution of the acylated nucleoside 35 (1 mmol) in abs. MeOH (5 mL) a sat. solution of NH$_3$ in MeOH (20 mL) was added dropwise at 0 °C. The mixture was stirred for another 30 min and left overnight at r.t. The solvent was removed under reduced pressure, and the formed material was kept for the next 24 h on a vacuum line. The resultant yellow material was purified by column chromatography on silica gel.

Yellow oil; yield: 0.27 g (74%); R$_f$ = 0.75; (EtOAc–hexane, 1:1).

1H NMR (DMSO-d$_6$): $\delta$ = 4.27 (m, 4 H, CH$_2$), 4.47 (br s, 2 H, OH), 4.54 (br m, 1 H, CH), 5.88 (br s, 2 H, CH$_2$), 7.79 (s, 1 H, CH), 8.44 (s, 1 H, CH).

13C NMR (DMSO-d$_6$): $\delta$ = 62.9, 71.0, 78.7, 115.4, 122.3 (q, $^1$J$_{CF}$ = 275 Hz), 126.0 (q, $^1$J$_{CF}$ = 275 Hz), 128.1 (q, $^1$J$_{CF}$ = 35 Hz), 133.9, 141.3 (q, $^1$J$_{CF}$ = 35 Hz), 149.1, 161.5.

MS (EI, 70 eV): m/z (%) = 597 [M$^+$] (13), 341 (17), 340 (100), 268 (31), 57 (59).

[(3aR,4R,6aS)-6-[5,7-Bis(trifluoromethyl)-3H-imidazol-4,5-b]-pyridin-3-yl]-2,2-dimethyltetrahydro-3H-cyclopenta[d][1,3]dioxol-4-yl-methanol (38)

Compound 38 was prepared according to a published procedure.$^{15}$

Yellow oil; yield: 0.48 g (57%); R$_f$ = 0.60 (hexane–EtOAc, 3:1).

1H NMR (DMSO-d$_6$): $\delta$ = 1.25 (s, 3 H, CH), 1.53 (s, 3 H, CH), 2.43–2.57 (br m, 3 H, CH), 3.72 (br m, 2 H, CH), 4.61 (dd, $^3$J$_{HH}$ = 6.0, 4.3 Hz, 1 H, CH), 4.85–4.91 (br m, 2 H, CH), 5.17 (dd, $^3$J$_{HH}$ = 6.8, 6.0 Hz, 1 H, CH), 7.71 (s, 1 H, CH), 8.13 (s, 1 H, CH).

13C NMR (DMSO-d$_6$): $\delta$ = 25.0, 27.7, 33.3, 45.0, 60.9, 61.5, 80.0, 83.4, 115.0, 116.3, 122.7 (q, $^1$J$_{CF}$ = 275 Hz), 128.3 (q, $^1$J$_{CF}$ = 275 Hz), 127.8 (q, $^1$J$_{CF}$ = 35 Hz), 133.9, 141.1 (q, $^1$J$_{CF}$ = 35 Hz), 149.9, 161.0.

MS (EI, 70 eV): m/z (%) = 425 [M$^+$] (17), 410 (12), 392 (33), 307 (25), 255 (21), 247 (37), 209 (67), 169 (100), 155 (67).

(1R,2S,3R,5R)-3-[5,7-Bis(trifluoromethyl)-3H-imidazol-4,5-b]-pyridin-3-yl]-5-(hydroxymethyl)cyclopentane-1,2-diol (39)

Compound 39 was obtained from 38 according to a published procedure.$^{16}$

References


(6) For ‘salvage’ synthesis, see, for example: (a) Manfredi, J. P.; Holmes, E. W. Annu. Rev. Physiol. 1985, 47, 691. (b) Berens, R. L.; Krug, E. C.; Marr, J. J.


