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Convenient synthesis of imidazo[1,5-*a*]pyrimidine derivatives and their unusual recyclization into 3*H*-imidazo[4,5-*b*]pyridine derivatives

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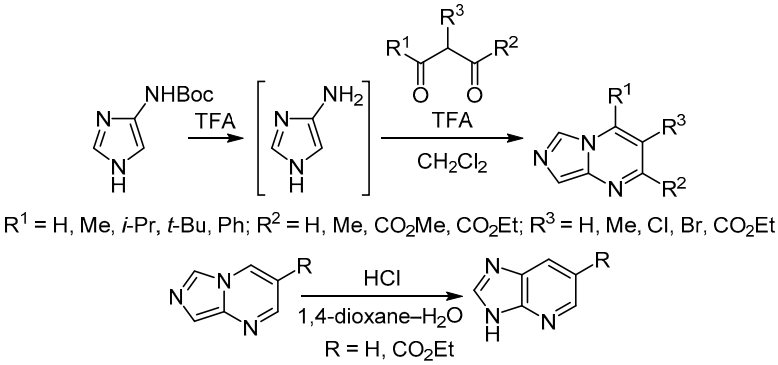


New derivatives of imidazo[1,5-*a*]pyrimidine have been synthesized by cyclization of *in situ* generated 1*H*-imidazol-4(5)-amine with 1,3-diketones or malondialdehyde derivatives. Utilization of asymmetrical 1,3-diketones leads to the formation of a mixture of regioisomers. The discovered conversion of imidazo[1,5-*a*]pyrimidine core into 3*H*-imidazo[4,5-*b*]pyridine that takes place only under acidic conditions can be considered as a new version of Dimroth rearrangement involving cleavage of C–N bond and formation of C–C bond.

Keywords: 1,3-diketones, 1*H*-imidazol-4(5)-amine, imidazo[4,5-*b*]pyridines, imidazo[1,5-*a*]pyrimidines, trifluoroacetic acid, carbonylation, Dimroth rearrangement.

Imidazopyrimidines are structural analogs (isosteres) of purine bases, e.g., adenine and guanine, and, particularly, have been evaluated and/or used as, to mention a few, non-benzodiazepine GABA receptor agonists,[1] p38 mitogen activated protein kinase inhibitors for treatment of rheumatoid arthritis,[2] or antibacterial agents.[3] As members of the imidazopyrimidines class, imidazo[1,5-*a*]pyrimidines are poorly represented in the literature, most probably, due to the difficulties in obtaining 1*H*-imidazol-4(5)-amine derivatives.[4]

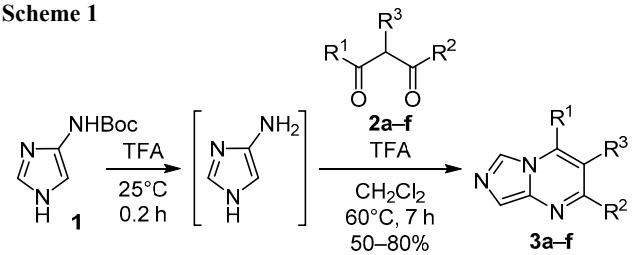
Synthetic approaches toward imidazo[1,5-*a*]pyrimidine core are based on application of 1*H*-imidazol-4(5)-amine derivatives and 1,3-biselectrophilic reagents, such as 1,3-diketones, as starting materials. Currently, there are reports on the synthesis of imidazo[1,5-*a*]pyrimidines from 5-amino-1*H*-imidazole-4-carboxamide,[5] 5-amino-1*H*-imidazole-4-carbonitrile,[6] ethyl 5-amino-1*H*-imidazole-2-carboxylate,[7] and 5-amino-2-methyl-1*H*-imidazole.[8] Only a few derivatives of imidazo[1,5-*a*]pyrimidine have been obtained using 1*H*-imidazol-4(5)-amine[9] due to its relative instability.[10]

When 1*H*-imidazol-4(5)-amine is generated *in situ* in the presence of 1,3-biselectrophilic reagents by catalytic reduction of 4(5)-nitro-1*H*-imidazole in EtOH, 5,5'-diimidazole derivatives are usually obtained as the major products.[11] 1*H*-Imidazol-4(5)-amine hydrochloride can be easily obtained from the respective Boc-protected amine,[12] however, in our studies, it has been found that isolation of 1*H*-imidazol-4(5)-amine is unnecessary.

In this report, we demonstrate the condensation reaction of *tert*-butyl (1*H*-imidazol-4(5)-yl)carbamate (**1**) and malondialdehyde (**2a**) or its derivatives **2b**–**e** in TFA as a convenient route toward 3-substituted imidazo[1,5-*a*]-pyrimidines **3a**–**e**. As mentioned above, the proposed method involves *in situ* generation of 1*H*-imidazol-4(5)-amine *via* TFA-catalyzed Boc deprotection under mild conditions followed by its condensation with malondialdehydes **2a**–**e**. Thus, 3-substituted imidazo[1,5-*a*]-pyrimidines **3a**–**e** were obtained in moderate to high yields (50–80%). Under the same conditions, 2,4-dimethyl-imidazo[1,5-*a*]pyrimidine (**3f**) was also obtained by the

condensation reaction of Boc-protected amine **1** and pentane-2,4-dione (**2f**) (Scheme 1).

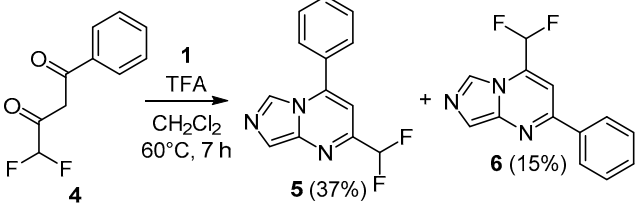
Scheme 1



a $R^1 = R^2 = H$, $R^3 = H$; **b** $R^1 = R^2 = H$, $R^3 = Me$
c $R^1 = R^2 = H$, $R^3 = Cl$; **d** $R^1 = R^2 = H$, $R^3 = Br$; **e** $R^1 = R^2 = H$, $R^3 = CO_2Et$; **f** $R^1 = R^2 = Me$, $R^3 = H$

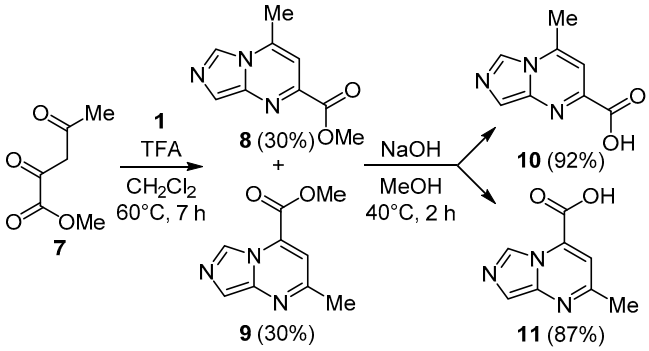
Using unsymmetrical 1,3-diketones, such as 4,4-difluoro-1-phenylbutane-1,3-dione (**4**), a mixture of regioisomers **5** and **6** (Scheme 2) was obtained and quantitatively separated using column chromatography. According to LCMS data, the ratio of regioisomers **5** and **6** was ca. 4:1.

Scheme 2



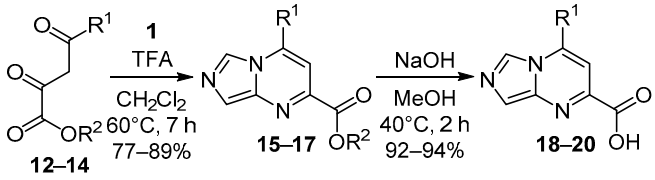
The interaction of amine **1** and methyl 2,4-dioxopentanoate (**7**) also afforded a mixture of regioisomers **8** and **9** in a ratio of 1:1. Base-promoted hydrolysis of the obtained esters **8** and **9** led to the formation of the corresponding carboxylic acids **10** and **11** that were isolated in high yields and purity (Scheme 3). The synthesis of methyl 2-methylimidazo[1,5-*a*]pyrimidine-4-carboxylate (**9**) in 1.4% yield has been described in patent literature.[13]

Scheme 3



Thus, it becomes evident that the ratio of regioisomers mainly depends on the nature of the substituents at the 1,3-diketone moiety. Noteworthy, the reaction of Boc-protected amine **1** and ethyl 5-methyl-2,4-dioxohexanoate (**12**), ethyl 5,5-dimethyl-2,4-dioxohexanoate (**13**), or methyl 2,4-dioxo-4-phenylbutanoate (**14**) led to the formation of only one regioisomer – ethyl 4-isopropylimidazo[1,5-*a*]-pyrimidine-2-carboxylate (**15**), ethyl 4-(*tert*-butyl)imidazo-[1,5-*a*]pyrimidine-2-carboxylate (**16**), and methyl 4-phenylimidazo[1,5-*a*]pyrimidine-2-carboxylate (**17**), respectively (Scheme 4). This phenomenon can be explained by the combination of sterical hindrances imposed by the isopropyl and *tert*-butyl groups and electronic factors of the ester moiety in compounds **12**–**14** that ensures exclusive interaction of β-keto group with amino group of the *in situ* formed 1*H*-imidazol-4(5)-amine. It should be noted that an attempt to obtain compound **17** from 1*H*-imidazol-4(5)-amine and methyl 2,4-dioxo-4-phenylbutanoate (**14**) was unsuccessful.[14]

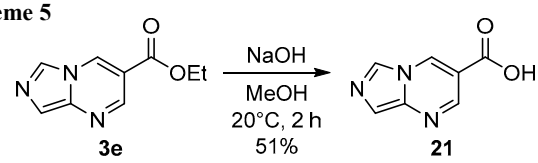
Scheme 4



12, **15** R^1 = *i*-Pr, R^2 = Et; **13**, **16** R^1 = *t*-Bu, R^2 = Et;
14, **17** R^1 = Ph, R^2 = Me; **18** R^1 = *i*-Pr; **19** R^1 = *t*-Bu; **20** R^1 = Ph

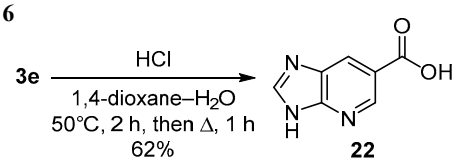
As in the case of compounds **8** and **9**, base-promoted hydrolysis of the obtained esters **15**–**17** afforded the corresponding carboxylic acids **18**–**20** in high yields and purity (Scheme 4). Basic hydrolysis of ester **3e** allowed to obtain imidazo[1,5-*a*]pyrimidine-3-carboxylic acid (**21**) (Scheme 5), although this chemical transformation was accompanied by the formation of undesired side products. A plausible explanation for the formation of one of the side products is a nucleophilic attack of the hydroxyl anion at C-4 atom of the pyrimidine ring and its subsequent opening similar to Dimroth ring opening.

Scheme 5



It is important to note, that the hydrolysis of ester **3e** under acidic conditions (2.5 N HCl in 1,4-dioxane–H_2O) exclusively led to the formation of isomeric 3*H*-imidazo-[4,5-*b*]pyridine-6-carboxylic acid (**22**) (Scheme 6).

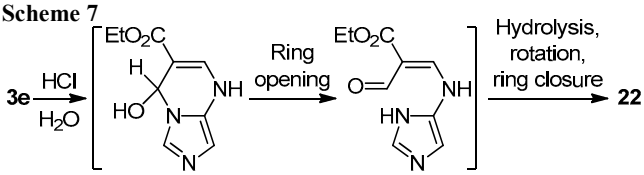
Scheme 6



The formation of 3*H*-imidazo[4,5-*b*]pyridine-6-carboxylic acid (**22**) is feasible *via* the addition of nucleophile, ring opening, and ring closure (ANRORC mechanism). In the case of compound **3e**, it proceeds in a similar way to the Dimroth rearrangement with the difference that Dimroth rearrangement involves cleavage of C–N bond and formation of new C–N bond, whereas our case is based on the cleavage of C–N bond and formation of C–C bond

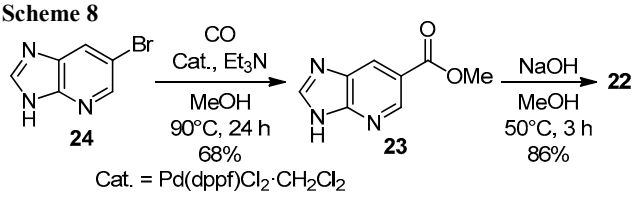
(Scheme 7). This rearrangement takes place only under acidic conditions.

Scheme 7



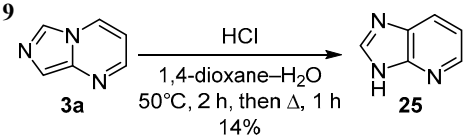
The structures of compounds **21** and **22** were confirmed by ^{1}H and ^{13}C NMR spectroscopy and by independent synthesis. Hence, 3*H*-imidazo[4,5-*b*]pyridine-6-carboxylic acid (**22**) was obtained by the hydrolysis of methyl 3*H*-imidazo[4,5-*b*]pyridine-6-carboxylate (**23**) resulting from the carbonylation of 6-bromo-3*H*-imidazo[4,5-*b*]-pyridine (**24**) in the presence of $Pd(dppf)Cl_2$ (Scheme 8).

Scheme 8



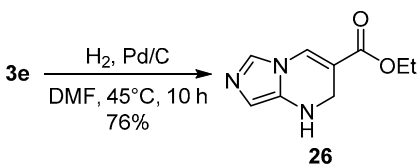
Apparently, the demonstrated rearrangement of imidazo-[1,5-*a*]pyrimidine **3e** to afford the respective 3*H*-imidazo-[4,5-*b*]pyridine **22** in acidic medium can be attributed also to other imidazo[1,5-*a*]pyrimidines. Particularly, refluxing of imidazo[1,5-*a*]pyrimidine **3a** in 10% HCl allowed to obtain 3*H*-imidazo[4,5-*b*]pyridine (**25**) in 14% yield (Scheme 9). NH_4Cl was also identified in the reaction mixture. The low yield of 3*H*-imidazo[4,5-*b*]pyridine (**25**) can be associated with the relative instability of amino-imidazole core in acidic medium.

Scheme 9



We also investigated the reduction of ethyl imidazo[1,5-*a*]-pyrimidine-3-carboxylate (**3e**) using H_2 over Pd/C. It was shown that selective hydrogenation takes place only over 10% Pd/C and leads to the formation of ethyl 1,2-dihydro-imidazo[1,5-*a*]pyrimidine-3-carboxylate (**26**) (Scheme 10). Based on NMR spectroscopy and LCMS data, other reducing agents, such as $NaBH_4$ and $LiBH_4$, afforded inseparable mixtures of reduced products including ones with reduced carboxylate group.

Scheme 10



In summary, we have developed a convenient route toward imidazo[1,5-*a*]pyrimidines by condensation of *in situ* generated 1*H*-imidazol-4(5)-amine with various malondialdehydes or 1,3-diketones. A novel rearrangement of imidazo[1,5-*a*]pyrimidine core involving cleavage of C–N bond and formation of C–C bond according to ANRORC mechanism and affording 3*H*-imidazo[4,5-*b*]-pyridine core was discovered.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance DRX-400 (400 and 100 MHz, respectively) and Bruker Avance DRX-500 (500 and 125 MHz, respectively) spectrometers. ^{19}F NMR spectra were recorded on a Bruker Avance DRX-500 spectrometer (470 MHz). TMS was used as internal standard. Mass spectra were recorded on an Agilent LC/MSD SL system (electrospray ionization at atmospheric pressure) equipped with a Zorbax SB-C18 column (4.6 × 15 mm, 1.8 μm), solvent DMSO. Elemental analyses were conducted using a varioMICROcube CHN-analyzer. Melting points were determined using a Fisher-Johns melting point apparatus.

All chemicals were purchased from Enamine Ltd.

***tert*-Butyl (1*H*-imidazol-4-yl)carbamate (1)**. A solution of 1*H*-imidazole-4-carbonyl azide[15] (55.2 g, 0.40 mol) in dry *tert*-BuOH (1 l) was refluxed for 10 h. The solvent was removed under reduced pressure, and the residue was dissolved in MeOH (1 l). The insoluble material was filtered off, and MeOH (500 ml) was evaporated. The mixture was cooled to room temperature, and the obtained solid was filtered off. Additional portion of product was acquired by concentration of the mother liquor until crystallization began. Yield 53.4 g (73%), white powder, mp 198–200°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 1.44 (9H, s, $C(CH_3)_3$); 6.90 (1H, s, H-5); 7.37 (1H, s, H-2); 9.98 (1H, s, NH); 11.82 (1H, s, NH). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 28.6 (3C); 78.8; 102.0; 131.8; 138.4; 153.2. Mass spectrum, *m*/*z* (I_{rel}, %): 184 $[M+H]^+$ (30), 128 $[M+H–CH_2=CMe_2]^+$ (100). Found, %: C 52.61; H 7.03; N 23.11. $C_8H_{13}N_3O_2$. Calculated, %: C 52.45; H 7.15; N 22.94.

Synthesis of imidazo[1,5-*a*]pyrimidines 3a–f, 5, 6, 8, 9, and 15–17 (General method). *tert*-Butyl (1*H*-imidazol-4-yl)carbamate (**1**) (1.83 g, 10 mmol) was added in portions to TFA (12 ml) at 10°C, and the mixture was stirred at 25°C for 0.2 h. A solution of 1,3-dicarbonyl compound **2a–f**, **4**, **7**, or **12–14** (10 mmol) in CH_2Cl_2 (10 ml) was added, and the resulting mixture was stirred at 60°C for 7 h. After completion of the reaction, TFA was evaporated under reduced pressure. The residue was diluted with 0.5 N $NaHCO_3$ (50 ml) and extracted with CH_2Cl_2 (100 ml). The organic layer was separated, washed with H_2O (50 ml), and dried with anhydrous Na_2SO_4. The obtained crude product was purified by crystallization or by flash column chromatography.

Imidazo[1,5-*a*]pyrimidine (3a). Yield 0.68 g (57%), yellow powder, mp 120°C (hexane). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 6.67–6.79 (1H, m, H-3); 7.48 (1H, s, H-8); 8.19 (1H, d, *J* = 5.0, H-2); 8.31 (1H, s, H-6); 8.71 (1H, d, *J* = 7.2, H-4). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 108.4; 119.4; 125.2; 129.2; 138.3; 146.1. Mass spectrum, *m*/*z* (I_{rel}, %): 120 $[M+H]^+$

(100). Found, %: C 60.37; H 4.11; N 35.39. $C_6H_5N_3$. Calculated, %: C 60.50; H 4.23; N 35.27.

3-Methylimidazo[1,5-*a*]pyrimidine (3b). Yield 0.67 g (50%), yellow powder, mp 124–125°C (hexane). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 2.28 (3H, s, CH_3); 7.59 (1H, s, H-8); 7.93–7.99 (2H, m, H-2,6); 8.04 (1H, s, H-4). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 15.5; 117.8; 119.3; 124.5; 125.9; 137.8; 149.2. Mass spectrum, *m*/*z* (I_{rel}, %): 134 $[M+H]^+$ (100). Found, %: C 63.29; H 5.16; N 31.77. $C_7H_7N_3$. Calculated, %: C 63.14; H 5.30; N 31.56.

3-Chloroimidazo[1,5-*a*]pyrimidine (3c). Yield 1.00 g (65%), yellow powder, mp 154–155°C (EtOH). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 7.69 (1H, s, H-8); 8.02 (1H, s, H-6); 8.08 (1H, s, H-2); 8.24 (1H, s, H-4). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 118.0; 120.9; 125.2; 126.1; 136.8; 145.4. Mass spectrum, *m*/*z* (I_{rel}, %): 156 $[M(^{37}Cl)+H]^+$ (45), 154 $[M(^{35}Cl)+H]^+$ (100). Found, %: C 46.78; H 2.55; N 27.51. $C_6H_4ClN_3$. Calculated, %: C 46.93; H 2.63; N 27.36.

3-Bromoimidazo[1,5-*a*]pyrimidine (3d). Yield 1.25 g (63%), yellow powder, mp 148–149°C (EtOH). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 7.61 (1H, s, H-8); 7.96 (1H, s, H-6); 8.06 (1H, s, H-2); 8.32 (1H, s, H-4). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 105.2; 120.9; 125.0; 128.4; 136.6; 146.7. Mass spectrum, *m*/*z* (I_{rel}, %): 200 $[M(^{81}Br)+H]^+$ (95), 198 $[M(^{79}Br)+H]^+$ (100). Found, %: C 36.51; H 2.10; N 21.38. $C_6H_4BrN_3$. Calculated, %: C 36.39; H 2.04; N 21.22.

Ethyl imidazo[1,5-*a*]pyrimidine-3-carboxylate (3e). Yield 1.53 g (80%), brown powder, mp 145–146°C (EtOH). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.34 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 4.35 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 7.58 (1H, s, H-8); 8.47 (1H, s, H-6); 8.50 (1H, s, H-2); 9.43 (1H, s, H-4). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 14.6; 61.8; 111.7; 119.0; 128.8; 136.1; 137.9; 145.8; 163.8. Mass spectrum, *m*/*z* (I_{rel}, %): 192 $[M+H]^+$ (100). Found, %: C 56.71; H 4.66; N 22.16. $C_9H_9N_3O_2$. Calculated, %: C 56.54; H 4.75; N 21.98.

2,4-Dimethylimidazo[1,5-*a*]pyrimidine (3f). Yield 0.85 g (58%), yellow powder, mp 136–137°C (hexane). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 2.41 (3H, s, 4-CH_3); 2.49 (3H, s, 2-CH_3); 6.25 (1H, s, H-3); 7.43 (1H, s, H-8); 7.83 (1H, s, H-6). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 17.5; 24.6; 108.8 (2C); 118.2; 122.3; 138.9; 155.5. Mass spectrum, *m*/*z* (I_{rel}, %): 148 $[M+H]^+$ (100). Found, %: C 65.44; H 6.00; N 28.74. $C_8H_9N_3$. Calculated, %: C 65.29; H 6.16; N 28.55.

2-Difluoromethyl-4-phenylimidazo[1,5-*a*]pyrimidine (5). Purified by flash column chromatography (SiO_2, eluent hexane–EtOAc, 20:3). Yield 0.91 g (37%), yellow powder, mp 119–120°C (hexane), R_f 0.24. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 6.52 (1H, t, *J* = 54.8, CHF_2); 6.82 (1H, s, H-3); 7.58–7.66 (3H, m, H-3',4',5'); 7.69–7.76 (2H, m, H-2',6'); 7.82 (1H, s, H-8); 8.27 (1H, s, H-6). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 103.4; 113.9 (t, *J* = 239.2, CHF_2); 122.1; 125.1; 127.8 (2C); 129.7 (2C); 131.1; 131.7; 138.2; 144.0; 148.8 (t, *J* = 27.8, C-2). ^{19}F NMR spectrum (470 MHz, $CDCl_3$), δ, ppm: –120 (s, CHF_2). Mass spectrum, *m*/*z* (I_{rel}, %): 246 $[M+H]^+$ (100). Found, %: C 63.81; H 3.59; N 17.28. $C_{13}H_9F_2N_3$. Calculated, %: C 63.67; H 3.70; N 17.14.

4-Difluoromethyl-2-phenylimidazo[1,5-*a*]pyrimidine (6). Purified by flash column chromatography (SiO_2, eluent hexane–EtOAc, 20:3). Yield 0.37 g (15%), yellow powder, mp 113–114°C (hexane), R_f 0.56. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 6.83 (1H, t, *J* = 52.8, CHF_2); 7.23 (1H, s, H-3); 7.40–7.50 (3H, m, H-3',4',5'); 7.77 (1H, s, H-8); 7.88–8.05 (2H, m, H-2',6'); 8.19 (1H, s, H-6). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 105.1 (t, *J* = 7.5); 110.8 (t, *J* = 242.6, CHF_2); 121.2; 124.4 (t, *J* = 2.5); 126.8 (2C); 129.0 (2C); 130.6; 133.2 (t, *J* = 25.1, C-4); 136.2; 139.1; 151.6. ^{19}F NMR spectrum (470 MHz, $CDCl_3$): –123.1 (s, CHF_2). Mass spectrum, *m*/*z* (I_{rel}, %): 246 $[M+H]^+$ (100). Found, %: C 63.49; H 3.62; N 17.22. $C_{13}H_9F_2N_3$. Calculated, %: C 63.67; H 3.70; N 17.14.

Methyl 4-methylimidazo[1,5-*a*]pyrimidine-2-carboxylate (8). Purified by flash column chromatography (SiO_2, eluent hexane–EtOAc, 20:3). Yield 0.57 g (30%), yellow powder, mp 183–184°C (hexane), R_f 0.62. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 2.67 (3H, s, CH_3); 4.00 (3H, s, CO_2CH_3); 7.20 (1H, s, H-3); 7.96 (1H, s, H-8); 8.13 (1H, s, H-6). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 17.9; 53.3; 106.7; 124.2; 124.5; 137.8; 139.6; 142.9; 164.5. Mass spectrum, *m*/*z* (I_{rel}, %): 192 $[M+H]^+$ (100). Found, %: C 56.42; H 4.62; N 22.11. $C_9H_9N_3O_2$. Calculated, %: C 56.54; H 4.75; N 21.98.

Methyl 2-methylimidazo[1,5-*a*]pyrimidine-4-carboxylate (9). Purified by flash column chromatography (SiO_2, eluent hexane–EtOAc, 20:3). Yield 0.57 g (30%), yellow powder, mp 145–146°C (hexane), R_f 0.38. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 2.55 (3H, s, CH_3); 4.00 (3H, s, CO_2CH_3); 7.21 (1H, s, H-3); 7.62 (1H, s, H-8); 8.95 (1H, s, H-6). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 24.5; 53.5; 113.6; 119.6; 127.0; 128.8; 139.7; 153.5; 161.6. Mass spectrum, *m*/*z* (I_{rel}, %): 192 $[M+H]^+$ (100). Found, %: C 56.71; H 4.60; N 21.89. $C_9H_9N_3O_2$. Calculated, %: C 56.54; H 4.75; N 21.98.

Ethyl 4-isopropylimidazo[1,5-*a*]pyrimidine-2-carboxylate (15). Yield 1.79 g (77%), yellow powder, mp 74–75°C (hexane). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.46 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 1.49 (6H, d, *J* = 6.5, $CH(C\underline{H}_3)_2$); 3.29–3.35 (1H, m, *J* = 6.5, $C\underline{H}(CH_3)_2$); 4.51 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 7.30 (1H, s, H-3); 8.01 (1H, s, H-8); 8.45 (1H, s, H-6). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 14.4; 19.6 (2C); 29.7; 62.5; 102.8; 124.0; 124.2; 138.1; 143.8; 149.5; 164.2. Mass spectrum, *m*/*z* (I_{rel}, %): 234 $[M+H]^+$ (100). Found, %: C 61.90; H 6.40; N 17.89. $C_{12}H_{15}N_3O_2$. Calculated, %: C 61.79; H 6.48; N 18.01.

Ethyl 4-(*tert*-butyl)imidazo[1,5-*a*]pyrimidine-2-carboxylate (16). Yield 2.15 g (87%), yellow powder, mp 123°C (hexane). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.44 (3H, t, *J* = 5.6, $CH_2C\underline{H}_3$); 1.58 (9H, s, $C(CH_3)_3$); 4.50 (2H, q, *J* = 5.6, $C\underline{H}_2CH_3$); 7.35 (1H, s, H-3); 8.03 (1H, s, H-8); 8.75 (1H, s, H-6). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm: 14.6; 26.9 (3C); 35.8; 62.2; 103.8; 122.1; 128.7; 138.9; 143.9; 152.2; 164.2. Mass spectrum, *m*/*z* (I_{rel}, %):

248 $[M+H]^+$ (100). Found, %: C 63.02; H 6.81; N 17.12. $C_{13}H_{17}N_3O_2$. Calculated, %: C 63.14; H 6.93; N 16.99.

Methyl 4-phenylimidazo[1,5-*a*]pyrimidine-2-carboxylate (**17**). Yield 2.25 g (89%), yellow powder, mp 199–200°C (CCl_4). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 4.03 (3H, s, CH_3); 7.31 (1H, s, H-3); 7.55–7.64 (3H, m, H-3',4',5'); 7.67–7.76 (2H, m, H-2',6'); 8.00 (1H, s, H-8); 8.35 (1H, s, H-6). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 53.4; 107.0; 124.6; 125.5; 127.8 (2C); 129.7 (2C); 131.1; 131.6; 138.6; 142.6; 143.4; 164.5. Mass spectrum, *m*/*z* (I_{rel}, %): 254 $[M+H]^+$ (100). Found, %: C 66.27; H 4.26; N 16.70. $C_{14}H_{11}N_3O_2$. Calculated, %: C 66.40; H 4.38; N 16.59.

Synthesis of carboxylic acids 10, 11, and 18–20 (General method). 2 N aqueous NaOH (8 ml, 16 mmol) was added to a solution of compound **8**, **9**, or **15**–**17** (10 mmol) in MeOH (50 ml), and the reaction mixture was stirred at 40°C for 2 h. Usually, sodium salt precipitated after a few minutes. MeOH was evaporated under reduced pressure, the residue was diluted with H_2O (80 ml), and the mixture was acidified to pH 5 using 2 N HCl. The obtained solid was filtered off. Products **10**, **11**, and **18**–**20** did not require additional purification (purity >95%, as evidenced by ^{1}H NMR spectroscopy and LCMS).

4-Methylimidazo[1,5-*a*]pyrimidine-2-carboxylic acid (10). Yield 1.63 g (92%), yellow powder, mp 300°C (decomp.). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 2.65 (3H, s, CH_3); 7.14 (1H, s, H-3); 7.78 (1H, s, H-8); 8.47 (1H, s, H-6); 13.40 (1H, s, CO_2H). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 17.7; 106.5; 122.5; 126.2; 137.9; 141.8; 144.4; 165.7. Mass spectrum, *m*/*z* (I_{rel}, %): 178 $[M+H]^+$ (100). Found, %: C 54.08; H 3.90; N 23.53. $C_8H_7N_3O_2$. Calculated, %: C 54.24; H 3.98; N 23.72.

2-Methylimidazo[1,5-*a*]pyrimidine-4-carboxylic acid (11). Yield 1.54 g (87%), yellow powder, mp 150°C (decomp.). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 2.48 (3H, s, CH_3); 7.32 (1H, s, H-3); 7.54 (1H, s, H-8); 8.94 (1H, s, H-6); 13.00 (1H, s, CO_2H). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 24.3; 113.3; 119.1; 128.1; 129.0; 140.4; 155.1; 162.3. Mass spectrum, *m*/*z* (I_{rel}, %): 178 $[M+H]^+$ (100). Found, %: C 54.11; H 3.87; N 23.61. $C_8H_7N_3O_2$. Calculated, %: C 54.24; H 3.98; N 23.72.

4-Isopropylimidazo[1,5-*a*]pyrimidine-2-carboxylic acid (18). Yield 1.89 g (92%), yellow powder, mp 260°C (decomp.). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.33 (6H, d, *J* = 6.8, $CH(C\underline{H}_3)_2$); 3.39–3.48 (1H, m, $C\underline{H}(CH_3)_2$); 7.08 (1H, s, H-3); 7.78 (1H, s, H-8); 8.63 (1H, s, H-6). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 19.8 (2C); 29.2; 102.6; 122.3; 126.0; 138.2; 145.8; 150.4; 166.0. Mass spectrum, *m*/*z* (I_{rel}, %): 206 $[M+H]^+$ (100). Found, %: C 58.71; H 5.32; N 20.30. $C_{10}H_{11}N_3O_2$. Calculated, %: C 58.53; H 5.40; N 20.48.

4-(*tert*-Butyl)imidazo[1,5-*a*]pyrimidine-2-carboxylic acid (19). Yield 2.04 g (93%), pale-yellow powder, mp 308–309°C (decomp.). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.45 (9H, s, $C(CH_3)_3$); 7.07 (1H, s, H-3); 7.84 (1H, s, H-8); 8.84 (1H, s, H-6); 13.00 (1H, s, CO_2H). ^{13}C NMR spectrum (125 MHz, DMSO-d_6), δ, ppm: 26.9 (3C); 35.6; 103.5; 122.4; 128.6; 139.0; 144.5; 151.8; 165.8. Mass spectrum, *m*/*z* (I_{rel}, %): 220 $[M+H]^+$ (100). Found, %: C 60.37; H 5.87; N 19.08. $C_{11}H_{13}N_3O_2$. Calculated, %: C 60.26; H 5.98; N 19.17.

4-Phenylimidazo[1,5-*a*]pyrimidine-2-carboxylic acid (20). Yield 2.25 g (94%), yellow powder, mp >300°C (decomp.). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 7.20 (1H, s, H-3); 7.59–7.66 (3H, m, H-3',4',5'); 7.84–7.89 (2H, m, H-2',6'); 7.91 (1H, s, H-8); 8.50 (1H, s, H-6); 13.62 (1H, s, CO_2H). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 107.1; 123.1; 126.3; 128.6 (2C); 130.0 (2C); 131.4; 131.8; 138.9; 142.7; 144.7; 165.5. Mass spectrum, *m*/*z* (I_{rel}, %): 240 $[M+H]^+$ (100). Found, %: C 65.10; H 3.70; N 17.71. $C_{13}H_9N_3O_2$. Calculated, %: C 65.27; H 3.79; N 17.56.

Imidazo[1,5-*a*]pyrimidine-3-carboxylic acid (21). 2 N aqueous NaOH (8 ml, 16 mmol) was added to a solution of ethyl imidazo[1,5-*a*]pyrimidine-3-carboxylate (**3e**) (1.90 g, 10 mmol) in MeOH (50 ml), and the reaction mixture was stirred at 20°C for 2 h. MeOH and H_2O were evaporated under reduced pressure, and the residue was redissolved in MeOH (100 ml). The insoluble material was filtered off, and the obtained filtrate was concentrated under reduced pressure. H_2O (50–60 ml) was added to the solid residue, and the mixture was acidified to pH 5 using 2 N HCl. The obtained solid was filtered off. Yield 0.83 g (51%), brown powder, mp >300°C (decomp.). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.23 (1H, s, H-8); 8.40 (1H, s, H-6); 8.59 (1H, s, H-2); 9.94 (1H, s, H-4). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 104.0; 112.6; 127.0; 132.9; 146.4; 156.6; 186.1. Mass spectrum, *m*/*z* (I_{rel}, %): 164 $[M+H]^+$ (100). Found, %: C 51.67; H 3.15; N 25.57. $C_7H_5N_3O_2$. Calculated, %: C 51.54; H 3.09; N 25.76.

3*H*-Imidazo[4,5-*b*]pyridine-6-carboxylic acid (22). Method I. A suspension of compound **3e** (3.80 g, 20 mmol) in 36% aqueous HCl (10 ml) and 1,4-dioxane (30 ml) was heated at 50°C for 2 h, then refluxed for 1 h. The reaction mixture was then concentrated under reduced pressure, and 1 N $NaHCO_3$ (50 ml) was added to the solid residue. The insoluble material was filtered off, and the filtrate was acidified to pH 5 using 1 N HCl. The obtained solid was filtered off.

Method II. A suspension of compound **23** (1.77 g, 10 mmol) in MeOH (50 ml) and 2 N aqueous NaOH (16 ml, 32 mmol) was stirred at 50°C for 3 h. MeOH was evaporated under reduced pressure, the residue was diluted with H_2O (60 ml), and the mixture was acidified to pH 5 using 2 N HCl. The obtained solid was filtered off. Yield 2.00 g (62%, method I), 1.40 g (86%, method II), brown powder, mp >300°C (decomp.). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 8.46 (1H, s, H-5); 8.59 (1H, s, H-7); 8.93 (1H, s, H-2); 13.35 (2H, s, NH, CO_2H). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 121.9; 125.5; 130.3; 146.0; 146.9; 154.2; 167.7. Mass spectrum, *m*/*z* (I_{rel}, %): 164 $[M+H]^+$ (100). Found, %: C 51.41; H 3.20; N 25.60. $C_7H_5N_3O_2$. Calculated, %: C 51.54; H 3.09; N 25.76.

6-Bromo-3*H*-imidazo[4,5-*b*]pyridine (24) was synthesized according to the procedure described in literature[16] from 5-bromopyridine-2,3-diamine (18.8 g, 0.10 mol) and triethyl orthoformate (90.0 g, 0.61 mol) in the presence of *p*-TsOH·H_2O (0.38 g, 2 mol %). Yield 17.2 g (87%), light-brown powder, mp 232–234°C (MeOH) (mp 223–225°C[16]). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 8.27 (1H, d, *J* = 1.6, H-5); 8.42 (1H, d, *J* = 1.6, H-7); 8.48 (1H, s, H-2); 13.25 (1H, br. s, NH). ^{13}C NMR spectrum (125 MHz, DMSO-d_6), δ, ppm: 113.2; 126.7; 132.4; 144.5; 146.0; 150.4. Mass spectrum, *m*/*z* (I_{rel}, %): 200 $[M(^{81}Br)+H]^+$ (95), 198 $[M(^{79}Br)+H]^+$ (100).

Methyl 3*H*-imidazo[4,5-*b*]pyridine-6-carboxylate (23). A mixture of 6-bromo-3*H*-imidazo[4,5-*b*]pyridine (**24**) (19.9 g, 0.10 mol), Et_3N (20.2 g, 0.20 mol), and Pd(dppf)Cl_2·CH_2Cl_2 (1.99 g, 10 mol %) in anhydrous MeOH (300 ml) was placed into a 500-ml stainless steel high pressure reactor. The reactor was closed, purged two times with CO, and pressurized with CO (45 bar) at room temperature. The reaction mixture was stirred at 90°C for 24 h. After completion of the reaction, the reactor was cooled to room temperature and the remaining CO was carefully vented. The solvent was evaporated under reduced pressure. The crude product was recrystallized from EtOH. Yield 12.0 g (68%), light-brown powder, mp 195°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 3.81 (3H, s, CH_3); 8.37 (1H, s, H-5); 8.56 (1H, s, H-7); 8.82 (1H, s, H-2); 13.35 (1H, s, NH). ^{13}C NMR spectrum (125 MHz, DMSO-d_6), δ, ppm: 52.6; 120.2; 145.5 (2C); 147.2 (3C); 166.3. Mass spectrum, *m*/*z* (I_{rel}, %): 178 $[M+1]^+$ (100). Found, %: C 54.40; H 4.09; N 23.64. $C_8H_7N_3O_2$. Calculated, %: C 54.24; H 3.98; N 23.72.

3*H*-Imidazo[4,5-*b*]pyridine (25) was synthesized according to the procedure for compound **22** (method I) from compound **3a** (1.19 g, 10 mmol). Yield 0.17 g (14%), yellow powder, mp 146–147°C (EtOAc) (mp 150–152°C[17]). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.19–7.28 (1H, m, H-6); 8.03 (1H, d, *J* = 8.0, H-5); 8.37 (1H, d, *J* = 4.0, H-7); 8.45 (1H, s, H-2); 13.03 (1H, s, NH). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 118.1; 124.4; 131.0; 144.1; 144.3; 151.3. Mass spectrum, *m*/*z* (I_{rel}, %): 120 $[M+H]^+$ (100). Found, %: C 60.39; H 4.14; N 35.34. $C_6H_5N_3$. Calculated, %: C 60.50; H 4.23; N 35.27.

Ethyl 1,2-dihydroimidazo[1,5-*a*]pyrimidine-3-carboxylate (26). A mixture of ethyl imidazo[1,5-*a*]pyrimidine-3-carboxylate (**3e**) (19.1 g, 0.10 mol) and 10% Pd/C (1.90 g, 10 mol %) in DMF (300 ml) was placed into a 500-ml stainless steel high pressure reactor. The reactor was closed, purged with H_2 two times, and pressurized with H_2 (20 bar) at room temperature. The reaction mixture was stirred at 45°C for 10 h. After completion of the reaction, the reactor was cooled to room temperature and the remaining H_2 was carefully vented. The reaction mixture was then heated to 80°C, and the catalyst was filtered off. After cooling to room temperature, H_2O (200 ml) was added and the obtained solid was filtered off and washed with H_2O (150 ml). The crude product was recrystallized from DMF. Yield 14.7 g (76%), colorless powder, mp 189°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.21 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 4.10 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 4.72 (2H, s, 2-CH_2); 6.37 (1H, s, H-4); 7.35 (1H, s, H-8); 7.40 (1H, s, H-6); 9.94 (1H, s, NH). ^{13}C NMR spectrum (125 MHz, DMSO-d_6), δ, ppm: 14.8; 40.8; 59.5; 91.3; 109.4; 128.6; 131.9; 135.1; 166.0. Mass spectrum, *m*/*z* (I_{rel}, %): 194 $[M+H]^+$ (100). Found, %: C 56.09; H 5.87; N 21.67. $C_9H_{11}N_3O_2$. Calculated, %: C 55.95; H 5.74; N 21.75.

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