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Short communication

Synthesis of 3-fluoroimidazo[1,2-*a*]pyrimidines and 5-fluoroimidazo[2,1-*b*][1,3]thiazoles via heterocyclization of (N-heteroarylimino) trifluoropyruvates

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ABSTRACT

Synthesis of 3-fluoroimidazo[1,2-*a*]pyrimidines and 5-fluoroimidazo[2,1-*b*][1,3]thiazoles was accomplished via triethyl phosphite-induced heterocyclization of the corresponding N-(heteroarylimino)trifluoropyruvates. This method provides a convenient approach to synthesize ring-fluorinated fused imidazoles of biological relevance.

1. Introduction

Aromatic fluorine is the best atomic modulator of biological properties of organic compounds [1]. As a result, fluorinated heteroaromatic compounds are becoming increasingly important in both agrochemistry and medicine [1–10]. Recent examples include A–B–C fluoroheterocyclic systems [11] suitable for cancer chemotherapy [12] (Fig. 1). Despite numerous publications in this field, development of efficient synthetic methods for the preparation of structurally diverse, ring-fluorinated heterocyclic compounds remains a challenging task [1].

2. Results and discussion

Burger et al. have shown that the reaction of hexafluoroacetone imines $(CF_3)_2C{=}N{-}C(R){=}X$ (X = O, S, NR^1), with tin(II) chloride leads to heterocyclization with the involvement of a trifluoromethyl group to yield 1,3-azole rings bearing a fluorine atom and a CF_3 group in neighboring positions [13]. It is also known that the reaction of methyl trifluoropyruvate 2-pyridylimines with trimethyl phosphite yields fluorinated imidazopyridines [14] (Scheme 1).

We expected that the extension of this strategy to trifluoropyruvate imines would allow preparation of valuable, ring-fluorinated, heterocyclic carboxylates. The required imines **1** were synthesized by reacting methyl trifluoropyruvate with 2-aminoheterocycles in the presence of thionyl chloride (Scheme 2).

Initially, we investigated reactions of imines **1** with tin(II) chloride. However, tin(II) chloride reduced the C=N bond to produce N-heteroaryl derivatives of trifluoroalanine (**3**) (Scheme 3) rather than the expected heterocyclization products (cf. [13,15,16]). The conversion **1**→**3** likely involves a [4+1] cycloaddition followed by hydrolysis of intermediate diazastannole **2**, which was detected in the reaction mixture via ^{19}F NMR. The most important ^{19}F NMR identification feature of the adduct **2** was the presence of satellites resulting from coupling with tin nuclei (δ_F −65 to −67.5 ppm, $^3J_{F-Sn}$ 73 Hz); the value of this spin–spin coupling is typical of CF_3–C–Sn fragments [15].

We subsequently found that imines **1a–d** reacted with triethyl phosphite to yield the desired fluorinated imidazothiazole **4a**,**b** and imidazopyrimidines **4c**,**d**, respectively (Scheme 4).

Both possible isomers, **4e** and **4f** (**4e**/**4f** 2:1), were formed in the reaction of unsymmetrical imine **1e** with triethyl phosphite (Scheme 5). Preferential cyclization involving the less sterically accessible pyrimidine nitrogen atom in imine **1e** is probably directed by the electron-donating inductive effect of the methyl group, which leads to enhanced nucleophilicity of the neighboring nitrogen atom.

Structure elucidation of the isomeric mixture **4e**,**f** was performed via comparison with NMR spectra of imidazopyrimidines **4c** and **4d**. Specifically, signals of 5-Me groups in ^1H NMR spectra of compounds **4d** and **4e** appear as doublets due to long

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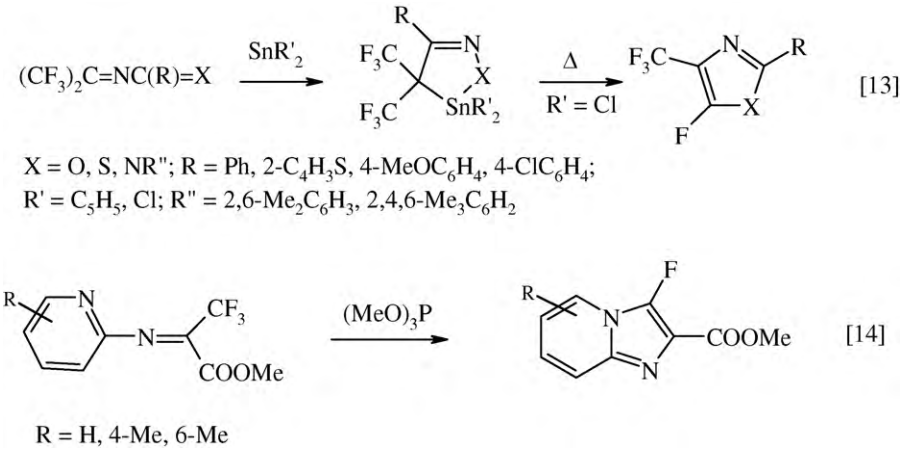


Scheme 1.

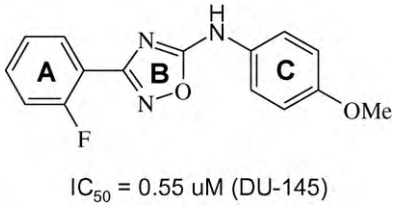
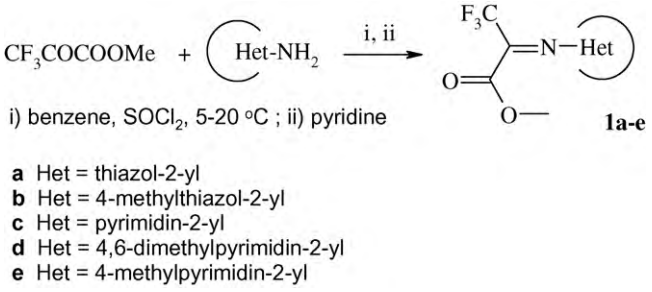


Fig. 1. An example of A-B-C heterocyclic system for prostate cancer chemotherapy.



Scheme 2.

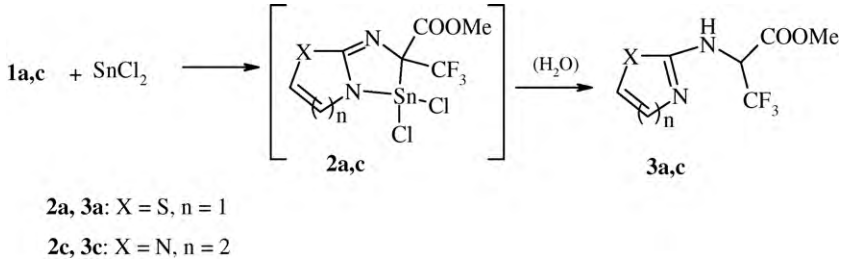
range coupling with the fluorine atom (δ 2.8 ppm, d, $^5J_{HF}$ 4.6 and 5.3 Hz), whereas 7-Me groups in compounds **4d** and **4f** appear as singlets at 2.57 and 2.66 ppm. Similarly, ^{19}F NMR signals appear as quartets (δ −137.3 and −138.2 ppm, $^5J_{FH}$ 4.5 and 5.3 Hz) or singlets (δ −142.2 and −143.2 ppm) in compounds **4d**,**e** and **4c**,**f**, respectively.

The reactions presented in the Schemes 4 and 5 proceed exothermically under very mild conditions (ether, room temperature). In addition, fluorinated heterocarboxylates **4** can be easily separated in practically pure form by simple filtration of the reaction mixtures.

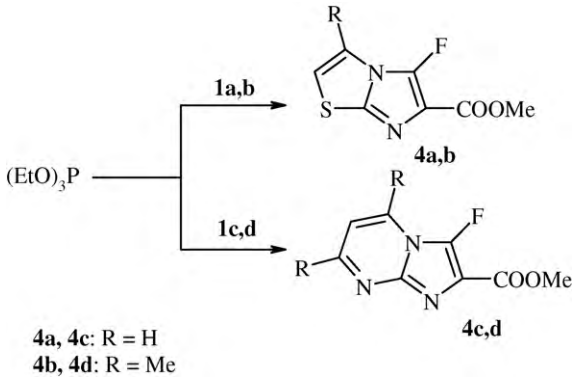
Analysis of the literature indicates that phosphorylation of polyfluoroalkylimines containing conjugated heterodiene systems leads initially to C-phosphorylation or/and [4+1] cycloaddition, followed by subsequent transformations of primary products [17]. We believe that the reaction of heteroarylimines **1** with triethyl phosphite proceeds in a similar manner (Scheme 6). Cheletropic 1,4-cycloaddition of triethyl phosphite produces unstable cyclic phosphoranes **5**. Dissociation of the P–C bond in **5** leads to the elimination of a fluoride anion from intermediate, bipolar ion **6**, followed by subsequent elimination of difluoro(triethoxy)phosphorane and intramolecular cyclization of activated difluoroethylene **7**, yielding the final products **4**. The validity of Scheme 6 was supported by ^{31}P and ^{19}F spectra monitoring of the reaction between imine **1a** and triethyl phosphite, which showed the appearance of two signals immediately after mixing of the reagents in ether ($\delta_P{}^1$ −68.5 ppm, $\delta_F{}^1$ −78.1 ppm; $\delta_P{}^2$ −77.1 ppm, $\delta_F{}^2$ −81.5 ppm; δ^1/δ^2 ~1:0.9). These signals could be attributed to stereoisomers of cyclic phosphorane **5** [18,19]. The decrease in intensity of these signals was accompanied by the appearance and increase in intensity of the difluoro(triethoxy)phosphorane signal (δ_P −74.5 ppm, t, $^1J_{PF}$ 728 Hz, δ_F −60.8 ppm, d, $^1J_{FP}$ 728 Hz) as well as precipitation of imidazothiazole **4a** from the reaction mixture.

It is conceivable that the first stages of the reactions of N-hetarylimines **1** with $SnCl_2$ and $(EtO)_3P$ are similar. The difference in the final products can be attributed to the difference in subsequent transformations of intermediate diazastannoles **2** (Scheme 2) and diazaphospholes **5** (Scheme 6).

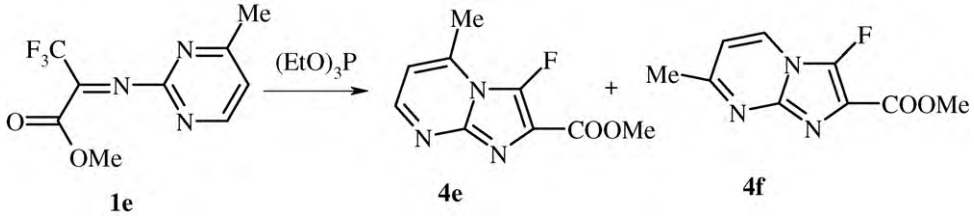
The spectral and analytical data of compounds **3** and **4** are in agreement with the proposed structures (see Section 4). The presence of C–F fragment in fluorinated heterocycles **4** is confirmed by ^{13}C NMR signals of C–F carbons (δ_C 144.7 and 141.6 ppm for **4a** and **4c**, respectively) with couplings typical of directly bonded fluorine atoms ($^1J_{CF}$ 289 Hz). The spin–spin interaction of the C-3 carbon with fluorine in **4a** (δ_C 115.2 ppm, d, $^3J_{CF}$ 2.5 Hz) further



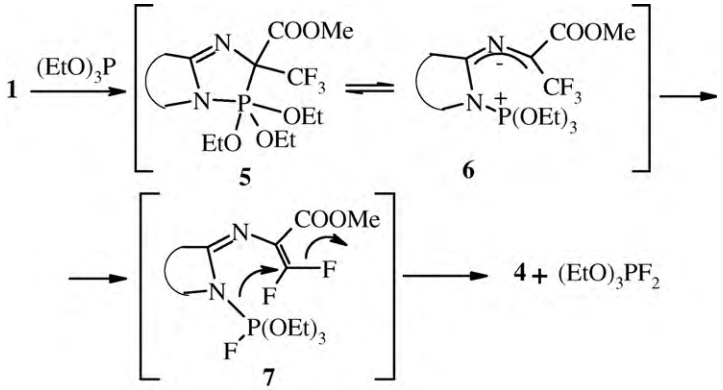
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

confirms the presence of a fused thiazole ring. The ^{19}F NMR spectra of compounds **4** show signals in the expected region.

3. Conclusions

In summary, we have developed an efficient method for the synthesis of imidazothiazoles and imidazopyrimidines bearing fluorine atoms and carboxyl functionalities in an imidazole ring from the corresponding trifluoropyruvate N-heteroarylimines.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer operating at 299.95 MHz. ^{19}F NMR spectra were recorded on a Gemini 200 Varian instrument operating at 188.14 MHz. ^{13}C NMR spectra were obtained on a Bruker Avance DRX 500 spectrometer operating at 125.76 MHz. Chemical shifts are reported in ppm relative to internal TMS (^{1}H, ^{13}C) and $CFCl_3$ (^{19}F) standards.

4.2. General procedure for preparation of iminocarboxylates (1)

Trifluoropyruvate (20 mmol) was added dropwise to a stirred suspension of an appropriate heteroarylamine (20 mmol) in benzene (20 mL) at room temperature. The reaction mixture spontaneously warmed and became homogeneous. After 1 h at room temperature, thionyl chloride (20 mmol) was added. After 15 min, pyridine (40 mmol) was added dropwise with stirring at 0 °C, and then the reaction mixture was allowed to warm to room temperature. Pyridine hydrochloride was filtered off, the solvent was evaporated under reduced pressure, and the residue was distilled to give iminocarboxylates **1**.

4.2.1. Methyl 2-[(thiazol-2-yl)imino]-3,3,3-trifluoropropanoate 1a

Yield 94%; bp 66 °C/0.07 Torr. ^{1}H NMR ($CDCl_3$) δ: 3.94 (3H, s, CH_3), 7.53 (1H, d, $^{3}J_{HH}$ = 3.3 Hz, 5-H), 7.75 (1H, d, $^{3}J_{HH}$ = 3.3 Hz, 4-H). ^{19}F NMR ($CDCl_3$) δ: −71.0. ^{13}C NMR ($CDCl_3$) δ: 53.38 (MeO), 118.50 (q, $^{1}J_{CF}$ = 278 Hz, CF_3), 124.34 (C-5), 142.55 (C-4), 147.94 (q, $^{2}J_{CF}$ = 37.7 Hz, C=N), 161.48, 165.12 (CO, C-2). Calc. for $C_7H_5F_3N_2O_2S$: C, 35.30, H, 2.12, F, 23.93, N, 11.76, S, 13.46%. Found: C, 35.74, H, 2.31, F, 23.64, N, 12.03, S, 13.62%.

4.2.2. Methyl 2-[(4-methylthiazol-2-yl)imino]-3,3,3-trifluoropropanoate **1b**

Yield 90%; bp 68 °C/0.07 Torr. ^{1}H NMR ($CDCl_3$) δ: 2.41 (3H, s, Me-C), 3.93 (3H, s, MeO), 7.12 (1H, s, 5-H). ^{19}F NMR ($CDCl_3$) δ: −69.74. Calc. for $C_8H_7F_3N_2O_2S$: C, 38.23, H, 2.97, N, 11.11%. Found: C, 38.10, H, 2.80, N, 11.22%.

4.2.3. Methyl 2-(pyrimidin-2-yl)imino]-3,3,3-trifluoropropanoate **1c**

Yield 90%; bp 71°C/0.07 Torr. ^{1}H NMR ($CDCl_3$) δ: 3.79 (3H, s, Me), 7.24 (1H, t, $^3J_{HH}$ = 4.8 Hz, 5-H), 8.76 (2H, d, $^3J_{HH}$ = 4.8 Hz, 4,6-H). ^{19}F NMR ($CDCl_3$) δ: −71.1. ^{13}C NMR ($CDCl_3$) δ: 53.29 (Me), 118.05 (q, $^1J_{CF}$ = 279 Hz, CF_3), 119.11 (C-5), 151.59 (q, $^2J_{CF}$ = 37.7 Hz, C=N), 158.22 (C-2), 158.53 (C-4,6), 163.88 (CO). Calc. for $C_8H_6F_3N_3O_2$: C, 41.21, H, 2.59, N, 18.02%. Found: C, 41.02, H, 2.34, N, 18.27%.

4.2.4. Methyl 2-[(4,6-dimethylpyrimidin-2-yl)imino]-3,3,3-trifluoropropanoate **1d**

Yield 90%; bp 97 °C/0.07 Torr. ^{1}H NMR ($CDCl_3$) δ: 2.50 (6H, s, Me-C), 3.80 (3H, s, MeO), 6.96 (1H, s, 5-H). ^{19}F NMR ($CDCl_3$) δ: −70.40. Calc. for $C_{10}H_{11}F_3N_2O_2S$: C, 45.98, H, 3.86, N, 16.09%. Found: C, 45.47, H, 3.62, N, 16.24%.

4.2.5. Methyl 2-[(4-methylpyrimidin-2-yl)imino]-3,3,3-trifluoropropanoate **1e**

Yield 90%; bp 87 °C/0.07 Torr. ^{1}H NMR ($CDCl_3$) δ: 2.56 (3H, s, Me-C), 3.79 (3H, s, MeO), 7.11 (1H, d, $^3J_{HH}$ = 5.4 Hz, 5-H), 8.57 (1H, d, $^3J_{HH}$ = 5.4 Hz, 6-H). ^{19}F NMR ($CDCl_3$) δ: −70. Calc. for $C_9H_8F_3N_3O_2$: C, 43.73, H, 3.26, N, 17.00%. Found: C, 43.51, H, 3.41, N, 16.83%.

4.3. General procedure for preparation of compounds **3a,c**

Tin(II) chloride (0.44 mmol) was added in one portion to a stirred solution of iminocarboxylates **1** (0.40 mmol) in THF (5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 3 h. Water (0.44 mmol) was added to the reaction mixture at 0 °C, and the mixture was stirred at room temperature for an additional 5 h. THF was evaporated under reduced pressure, and the remaining water solution was extracted with dichloromethane (10 mL). The organic phase was washed with water (3× 15 mL), dried ($MgSO_4$), and evaporated to afford trifluoroalaninates **3**.

4.3.1. Methyl (N-thiazol-2-yl)-3,3,3-trifluoroalaninate **3a**

Yield 90%; mp 88 °C. ^{1}H NMR ($CDCl_3$) δ: 3.89 (3H, s, Me), 5.38 (1H, q, $^3J_{HF}$ = 8.8 Hz, $CHCF_3$), 6.63 (1H, d, $^3J_{HH}$ = 4.2 Hz, 5-H), 7.15 (1H, d, $^3J_{HH}$ = 4.2 Hz, 4-H). ^{19}F NMR ($CDCl_3$) δ: −72.98 (q, $^3J_{FH}$ = 8.8 Hz). Calc. for $C_7H_7F_3N_2O_2S$: C, 35.00, H, 2.94, F, 23.73, N, 11.66, S, 13.35%. Found: C, 34.76, H, 3.07, F, 23.59, N, 11.52, S, 13.12%.

4.3.2. Methyl (N-pyrimidin-2-yl)-3,3,3-trifluoroalaninate **3c**

Yield 90%; ^{1}H NMR ($CDCl_3$) δ: 3.87 (3H, s, Me), 5.68 (1H, q, $^3J_{HF}$ = 7.8 Hz, $CHCF_3$), 6.69 (1H, t, $^3J_{HH}$ = 4.7 Hz, 5-H), 8.30 (2H, d, $^3J_{HH}$ = 4.7 Hz, 4,6-H). ^{19}F NMR ($CDCl_3$) δ: −73.00 (q, $^3J_{FH}$ = 7.8 Hz). Calc. for $C_8H_8F_3N_3O_2$: C, 40.86, H, 3.43, N, 17.87%. Found: $C_8H_8F_3N_3O_2$: C, 40.80, H, 3.54, N, 17.68%.

4.4. General procedure for preparation of compounds **4**

A solution of iminocarboxylate **1** (20 mmol) in diethyl ether (10 mL) was cooled to 0 °C. An equimolar amount of triethyl phosphite was added dropwise with vigorous stirring. The precipitated product was separated by filtration after 24 h.

4.4.1. Methyl 5-fluoroimidazo[2,1-b][1,3]thiazole-6-carboxylate **4a**

Yield 87%; mp 194–195 °C (dec.). ^{1}H NMR ($CDCl_3$) δ: 3.95 (3H, s, CH_3), 7.02 (1H, d, $^3J_{HH}$ = 4.2 Hz, 2-H), 7.38 (1H, d, $^3J_{HH}$ = 4.2 Hz, 3-H). ^{19}F NMR ($CDCl_3$) δ: −139.00. ^{13}C NMR ($CDCl_3$) δ: 51.95 (Me), 115.16 (d, $^3J_{CF}$ = 2.5 Hz, C-3), 116.29, 116.68 (C-2, C-6), 141.62 (d, $^3J_{CF}$ = 3.8 Hz, C-7a), 144.74 (d, $^1J_{CF}$ = 289 Hz, C-5), 161.57 (d, $^3J_{CF}$ = 6.3 Hz, CO). IR (KBr) 1720 (C=O) cm^{-1}. Calc. for $C_7H_5FN_2O_2S$: C, 42.00, H, 2.52, F, 9.49, N, 13.99, S, 16.02%. Found: C, 41.93, H, 2.47, F, 9.37, N, 13.75, S, 15.92%.

4.4.2. Methyl 5-fluoro-3-methylimidazo[2,1-b][1,3]thiazole-6-carboxylate **4b**

Yield 87%; mp 178–180 °C (dec.). ^{1}H NMR ($CDCl_3$) δ: 2.53 (3H, s, Me-C), 3.94 (3H, s, MeO), 6.50 (1H, s, 2-H). ^{19}F NMR ($CDCl_3$) δ: −141.75. ^{13}C NMR (DMSO-d_6) δ: 12.80 (d, $^4J_{CF}$ = 3 Hz, 3-Me), 51.86 (MeO), 111.30 (C-2), 115.62 (d, $^2J_{CF}$ = 1 Hz, C-6), 128.05 (d, $^3J_{CF}$ = 2 Hz, C-3), 142.04 (d, $^3J_{CF}$ = 4 Hz, C-7a), 146.05 (d, $^1J_{CF}$ = 287 Hz, C-5), 161.52 (d, $^3J_{CF}$ = 5 Hz, CO). Calc. for $C_8H_7FN_2O_2S$: C, 44.85, H, 3.29, N, 13.08%. Found: C, 44.79, H, 3.37, N, 12.97%.

4.4.3. Methyl 3-fluoroimidazo[1,2-a]pyrimidine-2-carboxylate **4c**

Yield 83%; mp >240 °C (dec.). ^{1}H NMR (DMSO-d_6) δ: 3.87 (3H, s, OMe), 7.16 (1H, m, 6-H), 8.65 (1H, m, 5-H), 8.74 (1H, m, 7-H). ^{19}F NMR (DMSO-d_6) δ: −142.18, m. ^{13}C NMR (DMSO-d_6) δ: 52.39 (MeO), 110.56 (C-6), 114.34 (C-2), 132.16 (C-5), 153.61 (C-7), 141.56 (d, $^1J_{CF}$ = 289 Hz, C-3), 150.70 (d, $^3J_{CF}$ = 4 Hz, C-8a), 161.85 (d, $^3J_{CF}$ = 4 Hz, C = O). Calc. for $C_8H_6FN_3O_2$: C, 49.24, H, 3.10, N, 21.53%. Found: C, 49.03, H, 3.21, N, 21.36%.

4.4.4. Methyl 3-fluoro-5,7-dimethylimidazo[1,2-a]pyrimidine-2-carboxylate **4d**

Yield 81%; mp >260 °C (dec.). ^{1}H NMR ($CDCl_3$) δ: 2.57 (3H, s, 7-Me), 2.76 (3H, d, $^5J_{HF}$ = 4.6 Hz, 5-Me), 3.98 (3H, s, OMe), 6.58 (1H, s, 6-H). ^{19}F NMR ($CDCl_3$) δ: −138.21 (q, $^5J_{FH}$ = 4.6 Hz). ^{13}C NMR (DMSO-d_6) δ: 17.01 (d, $^4J_{CF}$ = 6 Hz, 5-Me), 24.99 (7-Me), 52.20 (MeO), 111.56 (C-6), 113.84 (C-2), 140.02 (C-5), 143.26 (d, $^1J_{CF}$ = 291 Hz, C-3), 144.50 (d, $^3J_{CF}$ = 4 Hz, C-8a), 162.70 (d, $^3J_{CF}$ = 6 Hz, C=O), 163.85 (C-7). Calc. for $C_{10}H_{10}FN_3O_2$: C, 53.81, H, 4.52, N, 18.83%. Found: C, 53.57, H, 4.68, N, 18.72%.

4.4.5. Isomeric mixture of methyl 3-fluoro-5-methylimidazo[1,2-a]pyrimidine-2-carboxylate **4e** *and methyl 3-fluoro-7-methylimidazo[1,2-a]pyrimidine-2-carboxylate* **4f** *(***4e**/**4f** *2:1), yield 72%*

4e, ^{1}H NMR ($CDCl_3$) δ: 2.84 (3H, d, $^5J_{HF}$ = 5.3 Hz, 5-Me), 4.01 (3H, s, OMe), 6.71 (1H, d, $^3J_{HH}$ = 4.3 Hz, 6-H), 8.51 (1H, d, $^3J_{HH}$ = 4.3 Hz, 7-H). ^{19}F NMR ($CDCl_3$) δ:−137.35 (q, J_{HF} = 5.3 Hz).

4f, ^{1}H NMR ($CDCl_3$) δ: 2.66 (3H, s, 7-Me), 3.99 (3H, s, OMe), 6.99 (1H, d, $^3J_{HH}$ = 7.2 Hz, 6-H), 8.17 (1H, d, $^3J_{HH}$ = 7.2 Hz, 5-H). ^{19}F NMR ($CDCl_3$) δ: −143.17.

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