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An efficient method to access 2-fluoroalkylbenzimidazoles by PIDA oxidation of amidines

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ABSTRACT

A mild and practical strategy for the synthesis of 2-bromodifluoromethyl (or trifluoromethyl)-1*H*-benzimidazoles *via* PIDA-mediated oxidative intramolecular cyclization of the fluorinated amidines is described. The approach has the advantages of superior yields, excellent functional groups tolerance and mild reaction conditions.

1. Introduction

Benzimidazoles are known as an important class of heterocyclic compounds that exhibit a wide range of biological properties [1]. Among many 2-substituted benzimidazoles, 2-fluoroalkylbenzimidazole derivatives have received considerable attention due to their potential bioactivities such as antiviral, antifungal, antibacterial, antiparasitic and anti-tumor activities [2]. Recently, 2-trifluoromethyl-1*H*-benzimidazole derivatives with various 5- and 6-position bioisosteric substituents (–Cl, –F, $-CF_3$, and –CN), showed higher or equal activity against protozoa *Giardia intestinalis* and *Trichomonas vaginalis* in comparison with Albendazole and Metronidazole [3]. The classical methods generally used for the preparation of 2-fluoroalkylbenzimidazoles include the condensation of *ortho*-aminoanilines and reductive cyclization of *ortho*-nitroanilines with fluorinated carboxylic acids [4]. The drawbacks of these procedures are the limited diversity of the starting materials and harsh reaction conditions. Herein, we wish to describe a novel and facile synthesis of 2-bromodifluoromethyl (or trifluoromethyl)-1*H*-benzimidazoles by the reaction of PIDA (phenyliodine (III) diacetate) with *N*-arylbromodifluoro (or trifluoro)acetamidines.

2. Results and discussion

In 1995, Ramsden and Rose reported a reaction of *N*-substituted amidines with PIDA and found out that the nature of the amidine substituents and the reaction temperature determined the products [5]. Only four benzimidazole derivatives were synthesized by this approach. After that, the cyclization of amidines by oxidative means using iodine(III) compounds as reagents has not widely used owing to a rather narrow functional group tolerance. Recently, we described a mild method for the synthesis of *N*-substituted 2-fluoroalkylbenzimidazole *via* PIFA (phenyliodine (III) bis(trifluoroacetate))-mediated intramolecular cyclization of *N*,*N*′-disubstituted fluoroalkyl enthanimidamides [6]. It is only logical to extend our approach to the synthesis of *N*-*H*-2-fluoroalkylbenzimidazoles from *N*-arylfluoroacetamidines.

N-phenylbromodifluoroacetamidine **2a**, was chosen as a model substrate to optimize the reaction conditions, which was efficiently prepared by the reaction of 2-bromo-2,2-difluoro-*N*-phenylacetimidoyl chloride **1a** with ammonia in toluene at room temperature for 2 h [7]. When the substrate **2a** was treated with 1.2 equiv of PIDA in CH_3CN at room temperature for 12 h, 2-bromodifluoromethylbenzimidazole **3a** was formed in 82% yield. Whereas PIFA gave only 40% yield of **3a** under the similar conditions despite the starting material **2a** was consumed completely. Screening the solvents and the temperature revealed that **2a** was converted completely to the desired product **3a** in CH_3CN at 60 °C in 1 h. With the optimal reaction conditions in mind, we went ahead to explore the scope and limitations of this transformation. A series of substituted amidines which were synthesized from the corresponding imidoyl chlorides

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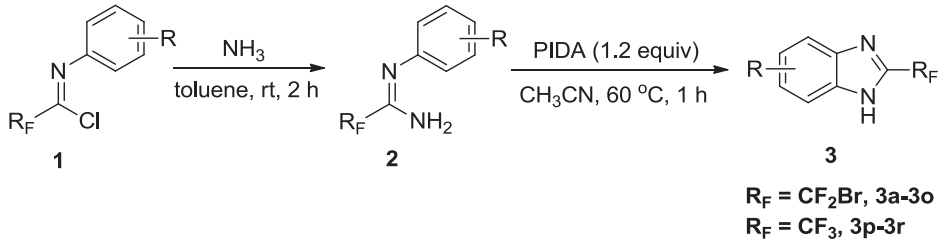
Table 1
Synthesis of 2-fluoroalkylbenzimidazoles.[a]



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Entry	R_F	Substrate (**1**)	**2**/yield (%)[b]	**3**/yield (%)[b]
1[c]	CF_2Br	H(**1a**)	**2a**/95	**3a**/82
2[c]	CF_2Br	*p*-Me(**1b**)	**2b**/98	**3b**/70
3[c]	CF_2Br	*p*-OMe(**1c**)	**2c**/97	**3c**/65
4	CF_2Br	*p*-I(**1d**)	**2d**/97	**3d**/65
5	CF_2Br	*p*-Br(**1e**)	**2e**/96	**3e**/87
6	CF_2Br	*p*-Cl(**1f**)	**2f**/94	**3f**/80
7	CF_2Br	*p*-CF_3(**1g**)	**2g**/96	**3g**/84
8	CF_2Br	*p*-CN(**1h**)	**2h**/89	**3h**/92
9	CF_2Br	*p*-Ac(**1i**)	**2i**/99	**3i**/97
10	CF_2Br	*p*-COOEt(**1j**)	**2j**/93	**3j**/95
11	CF_2Br	*p*-NO_2(**1k**)	**2k**/98	**3k**/94
12	CF_2Br	*o*-Me(**1l**)	**2l**/98	**3l**/83
13	CF_2Br	*o*-I(**1m**)	**2m**/96	**3m**/78
14	CF_2Br	*o*-CF_3(**1n**)	**2n**/97	**3n**/90
15[d]	CF_2Br	*m*-Me(**1o**)	**2o**/98	**3o**/88
16[d]	CF_2Br	*m*-CF_3(**1p**)	**2p**/97	**3p**/84
17	CF_3	*p*-CF_3(**1q**)	**2q**/97	**3q**/83
18	CF_3	*p*-CN(**1r**)	**2r**/98	**3r**/97

[a] Conditions: the amidines **2** (1 mmol), PIDA (386 mg, 1.2 mmol) in CH_3CN (10 mL) at 60 °C for 1 h.
[b] Isolated yields.
[c] At room temperature for 12 h.
[d] The ratio of 5(6):4(7) ≈ 1.5:1.

were treated with PIDA to afford 2-bromodifluoromethylbenzimidazoles in good yields. The results are summarized in Table 1. The substrates bearing the electron-donating (Me, OMe, entries 2, 3 and 12) and electron-withdrawing groups (CF_3, CN, Ac, COOEt, NO_2, entries 7–11 and 14) in the *para* or *ortho* position of the benzene ring led to the corresponding benzimidazoles in good yields. Halogens could survive under the reaction conditions, providing a useful handle for further cross-coupling reactions (entries 4–6 and 13) [8]. The intramolecular cyclization of *meta*-substituted amidines furnished a mixture of 5(6)-substituted and 4(7)-substituted regioisomers (entries 15 and 16). 5(6)-Substituted ones were detected as the major products, but the isomers could not be isolated by silica gel column chromatography. It is worth noting that 2,5(6)-ditrifluoromethylbenzimidazole **3q** and 5(6)-cyano-2-trifluoromethylbenzimidazole **3r** which were described above as potential antiprotozal agents were obtained in good yields by utilizing this method (entries 17 and 18).

3. Conclusion

In conclusion, we have successfully developed an efficient method for the generation of 2-fluoroalkyl-1*H*-benzimidazoles by the PIDA oxidation of fluorinated amidines. The process has obviated using *ortho*-aminoanilines and *ortho*-haloanilines as the starting materials. The biological study of the benzimidazoles obtained in this paper is currently underway.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer (300 MHz) with TMS as internal standard. ^{19}F NMR spectra were taken on a Bruker AM-300 (282 MHz) spectrometer using $CFCl_3$ as external standard. ^{13}C NMR spectra were taken on a Bruker AM-400 (100 MHz) spectrometer. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. All reagents were used as received from commercial sources. Column chromatography over silica gel (300–400 mesh) and petroleum ether/ethyl acetate combination was used as the eluent.

4.2. General procedure for the synthesis of fluorinated amidines 2

To a stirred mixture of fluorinated acetimidoyl chlorides **1** (3 mmol) in toluene (20 mL), the gas of ammonia was aerated slowly. The mixture was stirred at room temperature for 30 min and then filtered, washed by ethyl ether, after removing the solvent under reduced pressure, the product **2** was obtained quantitatively by flash column chromatography.

4.3. Spectroscopic data of 2-bromodifluoro (or trifluoro)-N-arylacetamidines 2

4.3.1. 2-Bromo-2,2-difluoro-N-phenylacetamidine (2a)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.34 (m, 2H), 7.11 (t, J = 7.2 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 4.89 (brs, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −57.45 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.9 (t, J = 26.0 Hz), 146.2, 129.6, 124.3, 120.5, 113.0 (t, J = 305.9 Hz). MS (EI): m/z (%): 248 (17.31) [M^+], 119 (100.00). Anal. Calcd. for $C_8H_7BrF_5N_2$: C, 38.58; H, 2.83; N, 11.25; Found: C, 38.91; H, 2.66; N, 11.23. IR (film): ν 3440, 3320, 3181, 1728, 1678, 1594, 1499, 1238, 1130, 933 cm^{-1}.

4.3.2. 2-Bromo-2,2-difluoro-N-p-tolylacetamidine (2b)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14 (d, J = 7.8 Hz, 2H), 6.80 (d, J = 7.8 Hz, 2H), 4.92 (brs, 2H) 2.31 (s, 3H). ^{19}F NMR (282 MHz,

$CDCl_3$): δ −57.32 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0, 143.3, 133.7, 130.1, 120.4, 113.0 (t, *J* = 305.9 Hz). MS (EI): *m*/*z* (%): 262 (23.00) [M^+], 133 (100.00). Anal. Calcd. for $C_9H_9BrF_2N_2$: C, 41.09; H, 3.45; N, 10.65; Found: C, 41.41; H, 3.40; N, 10.49. IR (film): ν 3442, 3329, 3147, 1673, 1506, 1242, 1170, 1121, 934 cm^{-1}.

*4.3.3. 2-Bromo-2,2-difluoro-N-(4-iodophenyl)acetamidine (**2d**)*

White solid, mp: 96 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.4 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 2H), 4.93 (brs, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −57.62 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0 (t, *J* = 26.0 Hz), 145.9, 138.6, 122.8, 112.8 (t, *J* = 305.2 Hz), 88.0. MS (EI): *m*/*z* (%): 374 (38.79) [M^+], 245 (100.00). Anal. Calcd. for $C_8H_6BrF_2IN_2$: C, 25.63; H, 1.61; N, 7.47; Found: C, 25.75; H, 1.61; N, 7.51. IR (KBr): ν 3484, 3238, 3169, 1670, 1607, 1477, 1241, 1152, 1119, 1005, 919 cm^{-1}.

*4.3.4. 2-Bromo-N-(4-bromophenyl)-2,2-difluoroacetamidine (**2e**)*

White solid, mp: 52 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 4.88 (brs, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −57.68 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1 (t, *J* = 26.0 Hz), 145.2, 132.6, 122.4, 117.2, 112.8 (t, *J* = 305.9 Hz). MS (EI): *m*/*z* (%): 328 (40.81) [M^+], 197 (100.00). Anal. Calcd. for $C_8H_6Br_2F_2N_2$: C, 29.30; H, 1.84; N, 8.54; Found: C, 29.42; H, 1.64; N, 8.55. IR (KBr): ν 3462, 3345, 3177, 1731, 1675, 1483, 1244, 1170, 1127, 928 cm^{-1}.

*4.3.5. 2-Bromo-N-(4-chlorophenyl)-2,2-difluoroacetamidine (**2f**)*

^1H NMR (300 MHz, $CDCl_3$): δ 7.31 (d, *J* = 7.8 Hz, 2H), 6.84 (d, *J* = 7.8 Hz, 2H), 5.05 (brs, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −57.60 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2 (t, *J* = 26.0 Hz), 144.7, 129.6, 129.4, 121.9, 112.8 (t, *J* = 305.9 Hz). MS (EI): *m*/*z* (%): 282 (18.88) [M^+], 153 (100.00). HRMS (EI) Calcd. for $C_8H_6BrClF_2N_2$: 281.9371; Found: 281.9375. IR (film): ν 3455, 3253, 3138, 1667, 1485, 1403, 1246, 1163, 1130, 928 cm^{-1}.

*4.3.6. 2-Bromo-2,2-difluoro-N-(4-(trifluoromethyl)phenyl)acetamidine (**2g**)*

White solid, mp: 100–101 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 4.89 (brs, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −57.83 (s, 2F), −62.52 (s, 3F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2 (t, *J* = 26.0 Hz), 149.5, 126.8 (q, *J* = 3.7 Hz), 126.3 (q, *J* = 32.8 Hz), 124.0 (q, *J* = 271.0 Hz), 120.8, 112.6 (t, *J* = 300.6 Hz). MS (EI): *m*/*z* (%): 316 (14.71) [M^+], 187 (100.00). Anal. Calcd. for $C_9H_6BrF_5N_2$: C, 34.09; H, 1.91; N, 8.84; Found: C, 34.41; H, 1.91; N, 9.05. IR (KBr): ν 3458, 3259, 3146, 1670, 1611, 1512, 1324, 1165, 1123, 929 cm^{-1}.

*4.3.7. 2-Bromo-N-(4-cyanophenyl)-2,2-difluoroacetamidine (**2h**)*

White solid, mp: 180–182 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 5.70 (brs, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −57.40 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6, 150.6, 133.5, 121.8, 118.9, 112.8, 106.9. MS (EI): *m*/*z* (%): 273 (13.45) [M^+], 144 (100.00). Anal. Calcd. for $C_9H_6BrF_2N_3$: C, 39.44; H, 2.21; N, 15.33; Found: C, 39.81; H, 2.34; N, 15.46. IR (KBr): ν 3354, 3143, 2231, 1670, 1599, 1498, 1249, 1161, 1118, 931 cm^{-1}.

*4.3.8. N-(4-acetylphenyl)-2-bromo-2,2-difluoroacetamidine (**2i**)*

White solid, mp: 130–132 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.8 Hz, 2H), 7.13 (brs, 2H), 6.94 (d, *J* = 7.8 Hz, 2H), 2.53 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −51.87 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 151.9, 150.4 (t, *J* = 26.0 Hz), 132.5, 129.9, 120.8, 113.0 (t, *J* = 306.5 Hz), 26.2. MS (EI): *m*/*z* (%): 290 (44.22) [M^+], 161 (100.00). Anal. Calcd. for $C_{10}H_9BrF_2N_2O$: C, 41.26; H, 3.12; N, 9.62; Found: C, 41.74; H, 3.08; N, 9.81. IR (KBr): ν 3404, 3325, 3211, 1674, 1654, 1590, 1258, 1176, 1135, 918 cm^{-1}.

*4.3.9. Ethyl-4-(1-amino-2-bromo-2,2-difluoroethylideneamino)benzoate (**2j**)*

White solid, mp: 126–127 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 5.00 (brs, 2H), 4.34 (q, *J* = 6.9 Hz, 2H), 1.39 (t, *J* = 6.9 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −57.68 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 150.9, 149.6 (t, *J* = 26.0 Hz), 131.1, 126.0, 120.4, 112.8 (t, *J* = 305.9 Hz), 60.8, 14.1. MS (EI): *m*/*z* (%): 320 (27.44) [M^+], 191 (100.00). Anal. Calcd. for $C_{11}H_{11}BrF_2N_2O_2$: C, 41.14; H, 3.45; N, 8.72; Found: C, 41.39; H, 3.42; N, 8.71. IR (KBr): ν 3389, 3164, 2977, 1697, 1655, 1598, 1280, 1248, 1172, 1114, 920, 873 cm^{-1}.

*4.3.10. 2-Bromo-2,2-difluoro-N-(4-nitrophenyl)acetamidine (**2k**)*

White solid, mp: 168–170 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 8.7 Hz, 2H), 5.08 (brs, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −57.66 (s, 2F). ^{13}C NMR (100 MHz, d_6-DMSO): δ 155.3, 151.3 (t, *J* = 26.0 Hz), 143.3, 125.6, 122.4, 113.7 (t, *J* = 305.6 Hz). MS (EI): *m*/*z* (%): 293 (22.35) [M^+], 164 (100.00). Anal. Calcd. for $C_8H_6BrF_2N_3O_2$: C, 32.68; H, 2.06; N, 14.29; Found: C, 33.04; H, 1.96; N, 14.32. IR (KBr): ν 3392, 3301, 3157, 1670, 1589, 1507, 1343, 1248, 1176, 1127, 932, 874 cm^{-1}.

*4.3.11. 2-Bromo-2,2-difluoro-N-o-tolylacetamidine (**2l**)*

^1H NMR (300 MHz, $CDCl_3$): δ 7.19–7.12 (m, 2H), 7.03–7.00 (m, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 4.81 (brs, 2H), 2.10 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −57.37 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4 (t, *J* = 26.2 Hz), 144.4, 131.1, 129.2, 127.0, 124.4, 119.7, 113.0 (t, *J* = 304.8 Hz). MS (EI): *m*/*z* (%): 262 (20.25) [M^+], 133 (100.00). HRMS (EI) Calcd. for $C_9H_9BrF_2N_2$: 261.9917; Found: 261.9916. IR (film): ν 3457, 3306, 3169, 1670, 1597, 1484, 1242, 1170, 1126, 925, 800 cm^{-1}.

*4.3.12. 2-Bromo-2,2-difluoro-N-(2-iodophenyl)acetamidine (**2m**)*

White solid, mp: 78 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, *J* = 7.7 Hz, 1H), 7.35–7.30 (m, 1H), 6.86–6.80 (m, 2H), 4.87 (brs, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −57.46 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8 (t, *J* = 26.2 Hz), 139.7, 129.4, 125.8, 120.4, 112.6 (t, *J* = 307.5 Hz), 90.2. MS (EI): *m*/*z* (%): 374 (30.92) [M^+], 245 (100.00). Anal. Calcd. for $C_8H_6BrF_2IN_2$: C, 25.63; H, 1.61; N, 7.47; Found: C, 25.73; H, 1.47; N, 7.44. IR (KBr): ν 3465, 3238, 3157, 1678, 1599, 1458, 1148, 1126, 1013, 934, 829 cm^{-1}.

*4.3.13. 2-Bromo-2,2-difluoro-N-(2-(trifluoromethyl)phenyl)acetamidine (**2n**)*

^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.53–7.48 (m, 1H), 7.22–7.16 (m, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 4.88 (brs, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −57.99 (s, 2F); −63.00 (s, 3F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0 (t, *J* = 26.2 Hz), 144.9, 133.1, 127.1 (q, *J* = 6.0 Hz), 124.0, 123.6 (q, *J* = 271.2 Hz), 121.7 (q, *J* = 30.0 Hz), 112.7 (t, *J* = 305.5 Hz). MS (EI): *m*/*z* (%): 316 (16.71) [M^+], 187 (100.00). HRMS (EI) Calcd. for $C_9H_6BrF_5N_2$: 315.9635; Found: 315.9633. IR (film): ν 3500, 3406, 3312, 3186, 1682, 1603, 1488, 1452, 1319, 1170, 1125, 930 cm^{-1}.

*4.3.14. 2-Bromo-2,2-difluoro-N-m-tolylacetamidine (**2o**)*

^1H NMR (300 MHz, $CDCl_3$): δ 7.24–7.18 (m, 1H), 6.89 (d, *J* = 7.3 Hz, 1H), 6.72–6.66 (m, 2H), 5.00 (brs, 2H), 2.31 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −57.30 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8 (t, *J* = 30.7 Hz), 146.3, 139.6, 129.5, 125.1, 121.1, 117.4, 113.3 (t, *J* = 304.8 Hz). MS (EI): *m*/*z* (%): 262 (16.78) [M^+], 133 (100.00). HRMS (EI) Calcd. for $C_9H_9BrF_2N_2$: 261.9917; Found: 261.9919. IR (film): ν 3462, 3308, 3169, 1670, 1600, 1484, 1267, 1171, 1123, 933, 805 cm^{-1}.

4.3.15. 2,2,2-Trifluoro-N-(3-(trifluoromethyl)phenyl)acetamidine (2p)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49–7.44 (m, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.16 (s, 1H), 7.07 (d, J = 7.2 Hz, 1H), 5.07 (brs, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −62.56 (s, 3F), −73.02 (s, 3F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 146.0 (q, J = 36.0 Hz), 132.2 (q, J = 32.0 Hz), 124.0, 123.8 (q, J = 270.5 Hz), 121.2 (q, J = 3.6 Hz), 118.0 (q, J = 276.4 Hz), 117.6 (q, J = 3.7 Hz). MS (EI): m/z (%): 256 (49.45) [M^+], 187 (100.00). HRMS (EI) Calcd. for $C_9H_6F_6N_2$: 256.0435; Found: 256.0437. IR (film): ν 3492, 3317, 3181, 1678, 1608, 1449, 1331, 1163, 900 cm^{-1}.

4.3.16. 2,2,2-Trifluoro-N-(4-(trifluoromethyl)phenyl)acetamidine (2q)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 4.99 (brs, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −62.12 (s, 3F), −73.22 (s, 3F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4, 145.9 (q, J = 35.7 Hz), 126.9, 126.5 (q, J = 32.5 Hz), 124.1 (q, J = 269.9 Hz), 121.2, 117.9 (q, J = 276.4 Hz). MS (EI): m/z (%): 256 (68.06) [M^+], 187 (100.00). Anal. Calcd. for $C_9H_6F_6N_2$: C, 42.20; H, 2.36; N, 10.94; Found: C, 42.52; H, 2.30; N, 11.13. IR (film): ν 3489, 3362, 3197, 1736, 1685, 1612, 1527, 1462, 1327, 1162, 1115, 1065, 833 cm^{-1}.

4.3.17. N-(4-Cyanophenyl)-2,2,2-trifluoroacetamidine (2r)

White solid, mp: 160–161 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J = 7.8 Hz, 2H), 7.03 (d, J = 7.8 Hz, 2H), 5.07 (brs, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −73.18 (s, 3F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 146.2 (q, J = 35.2 Hz), 133.4, 121.9, 118.8, 118.0 (q, J = 276.9 Hz), 106.4. MS (EI): m/z (%): 213 (72.18) [M^+], 144 (100.00). Anal. Calcd. for $C_9H_6F_3N_3$: C, 50.71; H, 2.84; N, 19.71; Found: C, 50.92; H, 2.73; N, 19.91. IR (KBr): ν 3473, 3342, 3149, 2243, 1686, 1601, 1498, 1264, 1150, 870 cm^{-1}.

4.4. General procedure for the synthesis of 2-fluoroalkylbenzimidazoles 3

A mixture of fluoroacetamidine **2** (1.0 mmol) and PIDA (386 mg, 1.2 mmol) in CH_3CN (10 mL) was stirred at 60 °C for 1 h. Then the mixture was concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to provide the desired product **3**.

4.5. Spectroscopic data of 2-fluoroalkylbenzimidazoles 3

4.5.1. 2-(Bromodifluoromethyl)-1H-benzo[d]imidazole (3a) [4b]

^{1}H NMR (300 MHz, d_6-DMSO): δ 13.90 (brs, 1H), 7.68–7.65 (m, 2H), 7.35–7.31 (m, 2H). MS (EI): m/z (%): 246 (18.08) [M^+], 167 (100.00).

4.5.2. 2-(Bromodifluoromethyl)-6(5)-methyl-1H-benzo[d]imidazole (3b)

White solid, mp: 144 °C. ^{1}H NMR (300 MHz, d_6-DMSO): δ 7.57 (d, J = 8.4 Hz, 1H), 7.45 (s, 1H), 7.18 (d, J = 8.4 Hz, 1H), 2.44 (s, 3H). ^{19}F NMR (282 MHz, d_6-DMSO): δ −47.25 (s, 2F). MS (EI): m/z (%): 260 (12.56) [M^+], 181 (100.00). HRMS (EI) Calcd. for $C_9H_7BrF_2N_2$: 259.9761; Found: 259.9762. IR (KBr): ν 2927, 1445, 1319, 1152, 1118, 990, 885, 802 cm^{-1}.

4.5.3. 2-(Bromodifluoromethyl)-6(5)-methoxy-1H-benzo[d]imidazole (3c)

White solid, mp: 144–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, J = 9.0 Hz, 1H), 7.08 (d, J = 2.1 Hz, 1H), 7.03 (dd, J_1 = 9.0 Hz, J_2 = 2.1 Hz, 1H), 3.83 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −48.20 (s, 2F). MS (EI): m/z (%): 276 (11.86) [M^+], 197 (100.00). Anal. Calcd. for $C_9H_7BrF_2N_2O$: C, 39.01; H, 2.55; N, 10.11; Found: C, 38.88; H, 2.60; N, 10.29. IR (KBr): ν 3292, 1635, 1458, 1276, 1242, 1170, 1117, 995 cm^{-1}.

4.5.4. 2-(Bromodifluoromethyl)-6(5)-iodo-1H-benzo[d]imidazole (3d)

White solid, mp: 160–162 °C. ^{1}H NMR (300 MHz, d_6-DMSO): δ 13.90 (brs, 1H), 8.07 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H). ^{19}F NMR (282 MHz, d_6-DMSO): δ −48.17 (s, 2F). MS (EI): m/z (%): 372 (17.05) [M^+], 293 (100.00). HRMS (EI) Calcd. for $C_8H_4BrF_2IN_2$: 371.8571; Found: 371.8573. IR (KBr): ν 3022, 1531, 1431, 1302, 1135, 986, 887, 799 cm^{-1}.

4.5.5. 6(5)-Bromo-2-(bromodifluoromethyl)-1H-benzo[d]imidazole (3e)

White solid, mp: 180–182 °C. ^{1}H NMR (300 MHz, d_6-DMSO): δ 13.90 (brs, 1H), 7.93 (s, 1H), 7.68 (d, J = 8.7 Hz, 1H), 7.52 (dd, J_1 = 8.7 Hz, J_2 = 1.8 Hz, 1H). ^{19}F NMR (282 MHz, d_6-DMSO): δ −48.20 (s, 2F). MS (EI): m/z (%): 326 (26.61) [M^+], 245 (100.00). HRMS (EI) Calcd. for $C_8H_4Br_2F_2N_2$: 323.8709; Found: 323.8705. IR (KBr): ν 3015, 1525, 1480, 1432, 1306, 1234, 1135, 1123, 988, 807 cm^{-1}.

4.5.6. 2-(Bromodifluoromethyl)-6(5)-chloro-1H-benzo[d]imidazole (3f)

White solid, mp: 180–182 °C. ^{1}H NMR (300 MHz, d_6-DMSO): δ 7.70–7.65 (m, 2H), 7.33 (d, J = 8.4 Hz, 1H). ^{19}F NMR (282 MHz, d_6-DMSO): δ −47.42 (s, 2F). MS (EI): m/z (%): 280 (10.46) [M^+], 201 (100.00). Anal. Calcd. for $C_8H_4BrClF_2N_2$: C, 34.14; H, 1.43; N, 9.95; Found: C, 34.51; H, 1.53; N, 10.00. IR (KBr): ν 2925, 1531, 1435, 1308, 1134, 1122, 989, 809 cm^{-1}.

4.5.7. 2-(Bromodifluoromethyl)-6(5)-(trifluoromethyl)-1H-benzo[d]imidazole (3g)

White solid, mp: 170–172 °C. ^{1}H NMR (300 MHz, d_6-DMSO): δ 14.32 (brs, 1H), 8.13 (s, 1H), 7.91–7.70 (m, 2H). ^{19}F NMR (282 MHz, d_6-DMSO): δ −48.80 (s, 2F), −59.45 (s, 3F). MS (EI): m/z (%): 314 (10.93) [M^+], 235 (100.00). Anal. Calcd. for $C_9H_4BrF_5N_2$: C, 34.31; H, 1.28; N, 8.89; Found: C, 34.34; H, 1.36; N, 8.87. IR (KBr): ν 3031, 1464, 1337, 1158, 1128, 1052, 888 cm^{-1}.

4.5.8. 2-(Bromodifluoromethyl)-1H-benzo[d]imidazole-6(5)-carbonitrile (3h)

White solid, mp: 160–162 °C. ^{1}H NMR (300 MHz, d_6-DMSO): δ 14.41 (brs, 1H), 8.35 (s, 1H), 7.86–7.74 (m, 2H). ^{19}F NMR (282 MHz, d_6-DMSO): δ −49.10 (s, 2F). MS (EI): m/z (%): 271 (8.68) [M^+], 212 (100.00). Anal. Calcd. for $C_9H_4BrF_2N_3$: C, 39.73; H, 1.48; N, 15.45; Found: C, 39.67; H, 1.52; N, 15.69. IR (KBr): ν 3072, 2233, 1474, 1309, 1132, 1114, 997, 887 cm^{-1}.

4.5.9. 1-(2-(Bromodifluoromethyl)-1H-benzo[d]imidazol-6 (5)-yl)ethanone (3i)

White solid, mp: 134–135 °C. ^{1}H NMR (300 MHz, d_6-DMSO): δ 14.14 (brs, 1H), 8.41–7.67 (m, 3H), 2.67 (s, 3H). ^{19}F NMR (282 MHz, d_6-DMSO): δ −48.26 (s, 2F). MS (EI): m/z (%): 288 (22.21) [M^+], 209 (100.00). Anal. Calcd. for $C_{10}H_7BrF_2N_2O$: C, 41.55; H, 2.44; N, 9.69; Found: C, 41.77; H, 2.44; N, 9.67. IR (KBr): ν 3227, 1668, 1616, 1313, 1281, 1111, 992, 888, 801 cm^{-1}.

4.5.10. Ethyl-2-(bromodifluoromethyl)-1H-benzo[d]imidazole-6(5)-carboxylate (3j)

^{1}H NMR (300 MHz, d_6-DMSO): δ 14.19 (brs, 1H), 8.31 (s, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.79 (s, 1H), 5.85 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H). ^{19}F NMR (282 MHz, d_6-DMSO): δ −48.64 (s, 2F). MS (EI): m/z (%): 318 (10.54) [M^+], 239 (100.00). Anal. Calcd. for $C_{11}H_9BrF_2N_2O_2$: C, 41.40; H, 2.84; N, 8.78; Found: C, 41.49; H, 2.93;

N, 8.91. IR (KBr): ν 2991, 1708, 1456, 1320, 1287, 1108, 918, 751 cm^{-1}.

*4.5.11. 2-(Bromodifluoromethyl)-6(5)-nitro-1H-benzo[d]imidazole (**3k**)*

White solid, mp: 175–176 °C. ^1H NMR (300 MHz, d_6-DMSO): δ 14.57 (brs, 1H), 8.63 (s, 1H), 8.26–8.24 (m, 1H), 7.87 (d, J = 8.1 Hz, 1H). ^{19}F NMR (282 MHz, d_6-DMSO): δ −49.47 (s, 2F). MS (EI): m/z (%): 291 (10.77) [M^+], 212 (100.00). Anal. Calcd. for $C_8H_4BrF_2N_3O_2$: C, 32.90; H, 1.38; N, 14.39; Found: C, 33.35; H, 1.49; N, 14.71. IR (KBr): ν 3091, 2771, 1627, 1521, 1349, 1319, 1124, 992, 887, 740 cm^{-1}.

*4.5.12. 2-(Bromodifluoromethyl)-4(7)-methyl-1H-benzo[d]imidazole (**3l**)*

^1H NMR (300 MHz, d_6-DMSO): δ 7.48 (d, J = 8.1 Hz, 1H), 7.28–7.23 (m, 1H), 7.14 (d, J = 7.2 Hz, 1H), 2.56 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −47.30 (s, 2F). MS (EI): m/z (%): 260 (11.86) [M^+], 181 (100.00). HRMS (EI) Calcd. for $C_9H_7BrF_2N_2$: 259.9761; Found: 259.9759. IR (KBr): ν 2926, 1456, 1311, 1128, 1000, 890, 745 cm^{-1}.

*4.5.13. 2-(Bromodifluoromethyl)-4(7)-iodo-1H-benzo[d]imidazole (**3m**)*

White solid, mp: 154–155 °C. ^1H NMR (300 MHz, d_6-DMSO): δ 14.14 (brs, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.19 (t, J = 7.7 Hz, 1H). ^{19}F NMR (282 MHz, d_6-DMSO): δ −48.26 (s, 2F). MS (EI): m/z (%): 372 (18.08) [M^+], 293 (100.00). Anal. Calcd. for $C_8H_4BrF_2IN_2$: C, 25.76; H, 1.08; N, 7.51; Found: C, 25.83; H, 1.12; N, 7.74. IR (KBr): ν 3018, 1574, 1453, 1309, 1257, 1140, 1116, 997, 887 cm^{-1}.

*4.5.14. 2-(Bromodifluoromethyl)-4(7)-(trifluoromethyl)-1H-benzo[d]imidazole (**3n**)*

White solid, mp: 146–148 °C. ^1H NMR (300 MHz, d_6-DMSO): δ 14.35 (brs, 1H), 7.95 (s, 1H), 7.74–7.54 (m, 2H). ^{19}F NMR (282 MHz, d_6-DMSO): δ −48.64 (s, 2F), −59.57 (s, 3F). MS (EI): m/z (%): 314 (11.93) [M^+], 235 (100.00). Anal. Calcd. for $C_9H_4BrF_5N_2$: C, 34.31; H, 1.28; N, 8.89; Found: C, 34.18; H, 1.29; N, 9.22. IR (KBr): ν 3131, 1456, 1340, 1313, 1198, 1123, 996, 891, 758 cm^{-1}.

*4.5.15. 2,6(5)-Bis(trifluoromethyl)-1H-benzo[d]imidazole (**3q**) [3]*

^1H NMR (300 MHz, d_6-DMSO): δ 13.93 (brs, 1H), 8.16 (s, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H). ^{19}F NMR (282 MHz, d_6-DMSO): δ −59.78 (s, 3F), −63.42 (s, 3F). MS (EI): m/z (%): 254 (100.00) [M^+].

*4.5.16. 2-(Trifluoromethyl)-1H-benzo[d]imidazole-6(5)-carbonitrile (**3r**) [3]*

^1H NMR (300 MHz, d_6-DMSO): δ 15.01 (brs, 1H), 8.74 (s, 1H), 8.27–8.17 (m, 2H). ^{19}F NMR (282 MHz, d_6-DMSO): δ −62.91 (s, 3F). MS (EI): m/z (%): 211 (100.00) [M^+].

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