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Hypervalent Iodine(III) Promoted Direct Synthesis of Imidazo[1,2-*a*]pyrimidines

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An efficient and mild synthesis of imidazo[1,2-*a*]pyrimidine derivatives has been developed from readily available pyrimidyl arylamines or enamines through a hypervalent iodine-promoted intramolecular C–H bond cycloamination reaction. This protocol allows for the facile construction of biologically active bicyclic imidazo[1,2-*a*]pyrimidine skeletons as well as other imidazo[1,2-*a*]-type fused heterocycles.

Introduction

Transition-metal-catalyzed C–H bond functionalization and subsequent direct C–N bond formation have attracted increasing scientific interest in recent years[1] and found numerous applications in organic synthesis, chemical biology and materials science. Nevertheless, apart from high cost and harsh conditions, the contamination of heavy metals has limited their potential application in the pharmaceutical industry, despite their apparent virtue of efficiency and atom-economy. In this context, the development of new metal-free C–N bond formation reactions from non-prefunctionalized precursors, inspired by the gratifying achievements obtained thus far,[2] is desirable.

Hypervalent iodine reagents, owing to their mild reaction conditions and environmentally friendly behavior, have been developed as highly valuable reagents in synthetic chemistry and as key replacements of toxic heavy metals in many cases,[3] especially for those applications with metal contamination problems. Recently, significant achievements have been made in hypervalent iodine(III) promoted C–H bond amination reactions in both intermolecular and intramolecular manner,[4] the latter of which has provided efficient access to various nitrogen-containing heterocycles.[5]

Imidazo[1,2-*a*]pyrimidines are prevalent structural motifs in pharmaceutically and biologically active compounds (Figure 1).[6] Furthermore, they also served as precursors for 2-amino-imidazoles in organic synthesis.[7] Consequently, several synthetic methods have been developed for the synthesis of this class of molecules. Conventional methods involved the intermolecular cyclization of 2-aminopyrimidine derivatives with other precursors such as alkynes[8] and 2-halo carbonyl compounds or their equivalents,[6h,9] and condensation reaction of 2-amino-imidazole derivatives with enones.[6c] Multicomponent reactions of 2-aminopyrimidines with aldehydes and isocyanides also provide efficient access to this valuable scaffold.[10] Despite significant achievements in their synthesis, development of highly efficient approaches to diversified imidazo[1,2-*a*]pyrimidine derivatives from readily available starting materials continues to be an active and rewarding research area. Recently, Zhu and co-workers reported an elegant synthesis of imidazo[1,2-*a*]pyridines from readily accessible *N*-aryl-2-aminopyridines by catalysis of an in situ generated hypervalent iodine reagent by using 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as the indispensable solvent.[11] As a part of our continuing interests in the chemistry and biologically activity of pyrimidine-containing compounds,[12] we herein

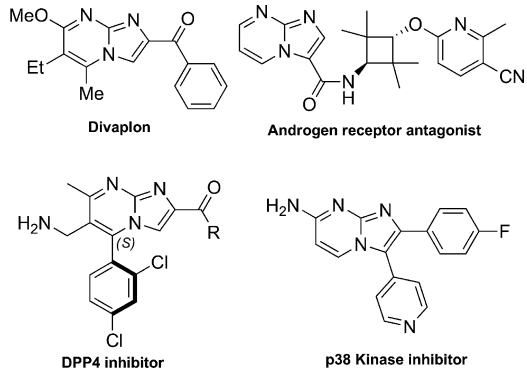

Figure 1. Bioactive compounds with imidazo[1,2-*a*]pyrimidine scaffolds.

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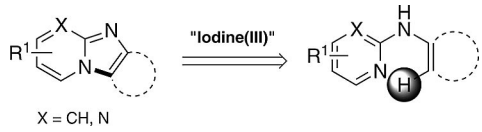
describe an efficient hypervalent iodine promoted intramolecular C–H bond cycloamination reaction to give imidazo[1,2-*a*]pyrimidine derivatives in good yields from readily available *N*-aryl-2-aminopyrimidines or pyrimidyl enamines. Furthermore, this protocol could be successfully applied to the corresponding pyridyl and pyrazyl counterparts (Scheme 1).



Scheme 1. Hypervalent iodine induced direct synthesis of imidazo[1,2-*a*] heterocycles.

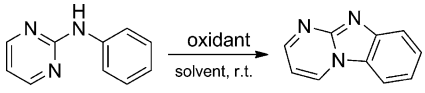
Results and Discussion

We began our study by examining the reaction of *N*-phenylpyrimidine-2-amine (**1a**) by using phenyliodine diacetate (PIDA) as oxidant at ambient temperature (Table 1). Solvents were found to be vital for this reaction. Among the solvents screened, acetonitrile afforded desired product **2a** in 72% yield after 4 h (Table 1, Entries 1–3). Addition of acetic acid as a co-solvent (CH_3CN/AcOH = 1:1, *v*/*v*; Table 1, Entry 4) or the use of copper triflate (10 mol-%) as an additive[13] (Table 1, Entry 5) only slightly improved the yields, whereas an increased yield could be achieved in the presence of both AcOH and copper triflate (Table 1, Entry 6). Gratifyingly, replacement of PIDA with phenyliodine bis(trifluoroacetate) (PIFA) significantly improved the yield to 88% in a much shorter reaction time (Table 1, Entry 7). However, in contrast to PIDA, use of PIFA in a mixture of CH_3CN and AcOH with or without copper triflate led to decreased yields (Table 1, Entries 8–9). In comparison, the hypervalent iodine(III) formed in situ from catalytic iodobenzene and stoichiometric *m*-chloroperbenzoic acid (*m*-CPBA), a strategy applied by Antonchick for the efficient intramolecular C(sp^2)–H bond amination reaction,[14] afforded either no desired product in CH_3CN (Table 1, Entry 10) or a very low yield with HFIP as solvent (Table 1, Entry 11).[11]

With optimized reaction conditions in hand, the scope and generality of the reaction were explored by using a series of *N*-phenylpyrimidin-2-amines. Most of the reactions were completed in 20 min to afford the desired products in moderate to good yields. As illustrated in Table 2, reactions of *N*-phenylpyrimidin-2-amines that bear various substitutions at the aniline moiety, regardless of their electronic properties, all gave imidazo[1,2-*a*] pyrimidines in good yields (**2b**–**2k**). It should be noted that a substrate with an iodo group was also compatible with the reaction conditions, affording **2e** in 64% yield. Substrates with *ortho* substitutions, which were often problematic owing to their steric hindrance, afforded desired products **2j** and **2k** in 53% and 78% yields, respectively. Pyrimidyl arylamines with substitutions on the pyrimidine moiety reacted smoothly to afford corresponding products **2l** and **2m**. To our delight, the current protocol could be further extended to the synthesis of imidazo[1,2-*a*]pyridines **2n** and **2o**, and imidazo[1,2-*a*]pyrazine **2p**, which would significantly expand the scope of its synthetic utility.

However, when (*E*)-ethyl 3-(pyrimidin-2-ylamino)-acrylate (**3a**) was used under the optimized conditions, only

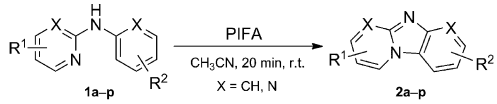
Table 1. Optimization of the reaction conditions.[a]

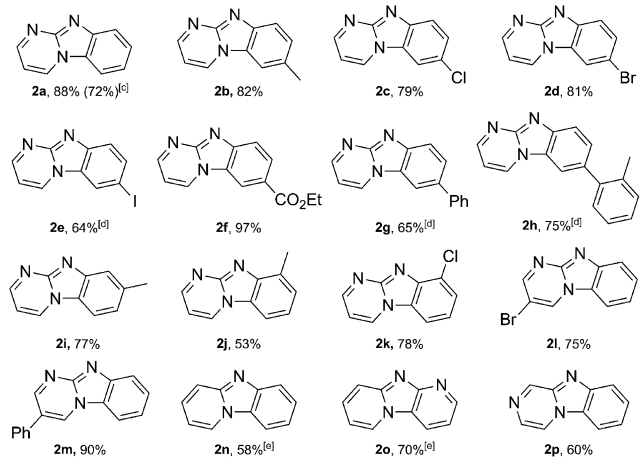


Entry	Oxidant [equiv.]	Solvent	Additive	Time [h]	Yield [%][b]
1	PIDA (1.5)	DMF	–	4	n.r.
2	PIDA (1.5)	DMSO	–	4	n.r.
3	PIDA (1.5)	CH_3CN	–	4	72
4	PIDA (1.5)	CH_3CN/AcOH	–	4	76
5	PIDA (1.5)	CH_3CN	$Cu(OTf)_2$	4	74
6	PIDA (1.5)	CH_3CN/AcOH	$Cu(OTf)_2$	4	83
7	**PIFA (1.5)**	**CH_3CN**	**–**	**0.3**	**88**
8	PIFA (1.5)	CH_3CN/AcOH	–	0.5	80
9	PIFA (1.5)	CH_3CN/AcOH	$Cu(OTf)_2$	4	79
10	PhI (0.1)/*m*-CPBA (1.2)	CH_3CN	–	24	n.r.
11	PhI (0.1)/*m*-CPBA (1.2)	HFIP	–	24	26

[a] Reaction conditions: **1a** (0.3 mmol), oxidant (1.5 equiv.), additive (10 mol-%) in solvent (1.5 mL), under air at room temperature. $Cu(OTf)_2$ = Copper triflate; n.r.: no reaction. [b] Isolated yield.

Table 2. Cyclization of *N*-aryl-2-aminopyrimidines.[a,b]

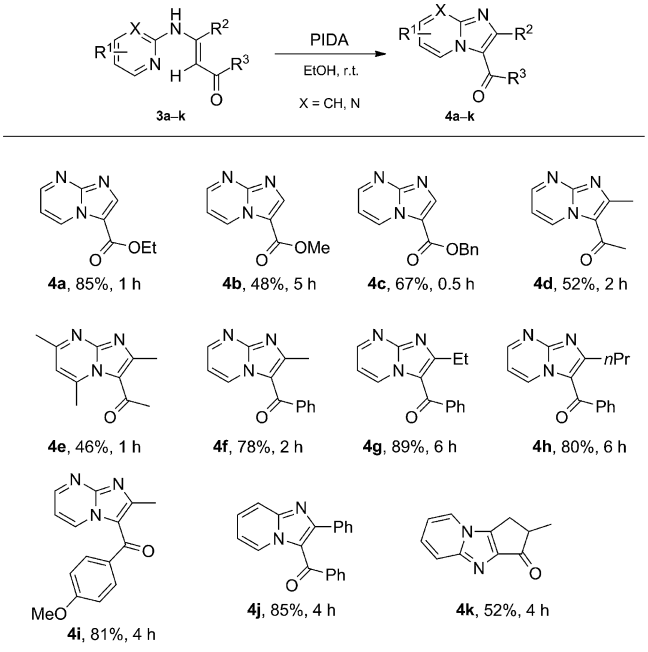




[a] Reaction conditions: **1a**–**1p** (0.3 mmol), PIFA (1.5 equiv.), CH_3CN (1.5 mL), 20 min, in air at room temperature. [b] Isolated yield. [c] On a one-gram scale. [d] Reacted for 25 min. [e] Reacted for 1 h.

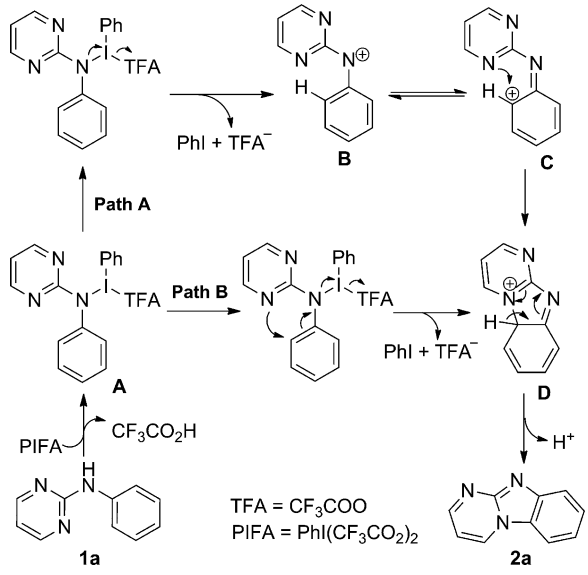
20% yield of desired product **4a** was afforded. To address this limitation and further explore the generality and scope of this approach, an extensive screening of oxidant, additive and solvent was then carried out. When PIDA was used instead of PIFA, the yield could be improved to 44%. Further screening of the solvents revealed that ethanol was the solvent of choice for this transformation, which afforded product **4a** in 85% yield (Table 3). After establishment of the appropriate conditions, a wide variety of pyrimidyl enamines **3a**–**3i**[15] were examined in this oxidative cyclization reaction, which leads to pharmaceutically interesting pyrimido[1,2-*a*]imidazoles **4a**–**4i** successfully. Pyrimidine-based β-enamino esters could give targeted pyrimido[1,2-*a*]imidazoles **4b** and **4c** in fair yields. Similarly, pyrimidine or pyridine derived β-enamino ketones afforded disubstituted compounds **4d**–**4j** in good yields, which are of potential pharmaceutical interests and otherwise not easily accessible by reported methods.[6h] In addition, cyclic enamino ketone, 5-methyl-2-(pyridin-2-ylamino)cyclopent-2-enone (**3k**), reacted smoothly to give tricyclic product **4k** in 52% yield.

Table 3. Cyclization of pyrimidinyl enamines.[a,b]



[a] Reaction conditions: **3a**–**3p** (0.3 mmol), PIDA (1.5 equiv.), EtOH (1.5 mL), in air at room temperature. [b] Isolated yield.

Although the reaction mechanism remains to be clarified, a plausible mechanism for this reaction was proposed in Scheme 2.[11,14,16] Nucleophilic substitution of the aniline nitrogen on the iodine(III) center of PIFA forms intermediate **A**, which is then transformed into nitrenium ion **B** through an oxidative process[14] and intermediate **B** is in resonance with carbocation form **C**. Subsequent nucleophilic attack of the pyrimidine nitrogen on the carbon cation center of intermediate **C** leads to cyclic intermediate **D**, which will generate desired product **2a** after a deprotonic rearomatization process (Scheme 2, Path A). Currently, direct nucleophilic attack of the pyrimidyl nitrogen atom on the aniline ring of **A** that leads to intermediate **D**,[11] with release of PhI and CF_3COO^- simultaneously, cannot be ruled out at this stage (Scheme 2, Path B).



Scheme 2. Plausible mechanism for synthesis of **2a** from **1a**.

Conclusions

In summary, we have developed a metal-free direct synthesis of imidazo[1,2-*a*]pyrimidine derivatives with high efficiency under mild reaction conditions from readily available starting materials. This reaction benefits from being environmentally benign, has good functional group tolerance and operational simplicity, which should make the current method of broad utility in the synthesis of diversified imidazo[1,2-*a*]-type fused heterocycles. Further exploration of this reaction and biological evaluation of the synthesized compounds are currently under investigation in our laboratory.

Experimental Section

General Methods: All reagents and metal catalysts were obtained from commercial sources without further purification, and commercially available solvents were purified before use. All new compounds were fully characterized. All melting points were taken on a WRS-1A or a WRS-1B Digital Melting Point Apparatus. Infrared spectra were obtained with an AVATAR 370 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AV-500 spectrometer operating at 500 and 125 MHz, respectively, with chemical shift values being reported relative to chloroform (δ = 7.26 ppm), dimethyl sulfoxide (δ = 2.50 ppm), acetone (δ = 2.05 ppm) or trimethylsilane (δ = 0.00 ppm) for ^{1}H NMR, and chloroform (δ = 77.16 ppm), dimethyl sulfoxide (δ = 39.52 ppm) or acetone (δ = 206.26, 29.84 ppm) for ^{13}C NMR spectroscopy. Mass spectra and high-resolution mass spectra were recorded with an Agilent 5975N by using an Electron impact (EI) or Electrospray ionization (ESI) techniques. Elemental analyses were carried out with an Elementar Vario EL elemental analyzer. Silica gel plate GF254 were used for thin layer chromatography (TLC) and silica

gel H or 300–400 mesh were used for flash column chromatography, yields refer to chromatographically and spectroscopically pure compounds, unless otherwise indicated.

General Procedure for the Synthesis of Imidazo[1,2-*a*]-Type Heterocycles 2a–2p, 4a–4k: To an oven-dried flask containing substrates (0.3 mmol, 1.0 equiv.) and oxidant (0.45 mmol, 1.5 equiv.), solvent (2.0 mL) was added. The reaction mixture was stirred at room temperature, which was monitored by TLC. Upon completion, the mixture was extracted with ethyl acetate (3× 10 mL). The combined organic phase was washed with brine and dried with Na_2SO_4. After that, the solid was filtered off through a thin pad of Celite, and the filtrate was evaporated in vacuo to give the crude product, which was purified by column chromatography on silica gel (ethyl acetate) to give imidazo[1,2-*a*]-fused heterocycles.

Benzo[4,5]imidazo[1,2-*a*]pyrimidine (2a):[17] Light yellow solid (44.7 mg, 88%), m.p. 205–207 °C. IR (KBr): $\tilde{\nu}$ = 3441, 3082, 1626, 1500, 1456, 1320 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.82 (d, J = 6.5 Hz, 1 H), 8.76 (s, 1 H), 7.98 (d, J = 8.0 Hz, 1 H), 7.89 (d, J = 8.5 Hz, 1 H), 7.55 (t, J = 7.5 Hz, 1 H), 7.38 (t, J = 7.5 Hz, 1 H), 6.91 (dd, J = 6.5, 4.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 155.6, 150.4, 143.9, 133.5, 126.7, 126.6, 122.2, 120.4, 110.8, 106.7 ppm. MS (EI): *m*/*z* (%) = 169 (30) [M^+], 154 (100).

7-Methylbenzo[4,5]imidazo[1,2-*a*]pyrimidine (2b): Light yellow solid (45.1 mg, 82%), m.p. 205–206 °C. IR (KBr): $\tilde{\nu}$ = 3421, 3045, 1606, 1499, 1452, 1376 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.79 (dd, J = 7.0, 2.0 Hz, 1 H), 8.75–8.74 (m, 1 H), 7.89 (d, J = 8.5 Hz, 1 H), 7.69 (s, 1 H), 7.39 (dd, J = 8.5, 1.0 Hz, 1 H), 6.92 (dd, J = 6.5, 4.0 Hz, 1 H), 2.56 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 155.1, 150.3, 142.2, 133.2, 132.5, 128.6, 126.9, 120.2, 110.4, 106.6, 22.0 ppm. MS (EI): *m*/*z* (%) = 183 (15) [M^+], 95 (100). HRMS (EI): *m*/*z* calcd. for $C_{11}H_9N_3$ [M^+] 183.0796; found 183.0791.

7-Chlorobenzo[4,5]imidazo[1,2-*a*]pyrimidine (2c): Light yellow solid (48.1 mg, 79%), m.p. 319–320 °C. IR (KBr): $\tilde{\nu}$ = 3051, 1615, 1524, 1498, 1460, 1201 cm^{-1}. ^1H NMR ([D$_6$]DMSO, 500 MHz): δ = 9.51 (dd, J = 6.5, 2.0 Hz, 1 H), 8.86 (q, J = 2.0 Hz, 1 H), 8.53 (d, J = 2.0 Hz, 1 H), 7.86 (d, J = 9.0 Hz, 1 H), 7.57 (dd, J = 8.5, 2.0 Hz, 1 H), 7.20 (dd, J = 6.5, 4.0 Hz, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 125 MHz): δ = 157.1, 150.7, 142.1, 136.1, 127.5, 126.4, 125.5, 120.6, 112.9, 107.3 ppm. MS (EI): *m*/*z* (%) = 205 (33) [M^+ (^{37}Cl)], 203 (100) [M^+ (^{35}Cl)], 154 (44). HRMS (EI): *m*/*z* calcd. for $C_{10}H_6N_3Cl$ [M^+] 203.0250; found 203.0248.

7-Bromobenzo[4,5]imidazo[1,2-*a*]pyrimidine (2d): Yellow solid (60.3 mg, 81%), m.p. 270–272 °C. IR (KBr): $\tilde{\nu}$ = 3095, 1625, 1523, 1497, 1459, 1202 cm^{-1}. ^1H NMR ([D$_6$]DMSO, 500 MHz): δ = 9.50 (dd, J = 6.5, 2.0 Hz, 1 H), 8.85 (q, J = 2.0 Hz, 1 H), 8.64 (d, J = 2.0 Hz, 1 H), 7.80 (d, J = 9.0 Hz, 1 H), 7.66 (dd, J = 9.0, 2.0 Hz, 1 H), 7.18 (dd, J = 7.0, 4.0 Hz, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 125 MHz): δ = 157.1, 150.5, 142.4, 136.1, 129.0, 128.0, 120.9, 115.8, 113.1, 107.4 ppm. MS (EI): *m*/*z* (%) = 249 (95) [M^+ (^{81}Br)], 247 (100) [M^+ (^{79}Br)]. HRMS (EI): *m*/*z* calcd. for $C_{10}H_6N_3Br$ [M^+] 246.9745; found 246.9747.

7-Iodobenzo[4,5]imidazo[1,2-*a*]pyrimidine (2e): Yellow solid (57.2 mg, 64%), m.p. 328–330 °C. IR (KBr): $\tilde{\nu}$ = 3024, 1624, 1524, 1497, 1205, 807 cm^{-1}. ^1H NMR ([D$_6$]DMSO, 500 MHz): δ = 9.50 (dd, J = 6.5, 1.5 Hz, 1 H), 8.85 (d, J = 1.5 Hz, 1 H), 8.78 (s, 1 H), 7.80 (d, J = 8.5 Hz, 1 H), 7.67 (d, J = 8.5 Hz, 1 H), 7.17 (dd, J = 6.5, 4.5 Hz, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 125 MHz): δ = 157.6, 149.7, 141.5, 136.4, 134.8, 128.4, 121.6, 120.7, 107.9, 84.7 ppm. MS (EI): *m*/*z* (%) = 295 (100) [M^+], 296 (13). HRMS (EI): *m*/*z* calcd. for $C_{10}H_6N_3I$ [M^+] 294.9606; found 294.9604.

Ethylbenzo[4,5]imidazo[1,2-*a*]pyrimidine-7-carboxylate (2f): Yellow solid (70.1 mg, 97%), m.p. 260–262 °C. IR (KBr): $\tilde{\nu}$ = 3061, 1708, 1606, 1501, 1453, 1380 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.90–8.88 (m, 2 H), 8.67 (d, J = 1.0 Hz, 1 H), 8.27 (dd, J = 8.5, 1.5 Hz, 1 H), 8.01 (d, J = 8.5 Hz, 1 H), 7.03 (dd, J = 6.5, 4.5 Hz, 1 H), 4.44 (q, J = 7.0 Hz, 2 H), 1.44 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 166.5, 156.9, 152.4, 147.5, 133.9, 127.7, 126.7, 124.3, 120.2, 113.4, 107.6, 61.4, 14.5 ppm. MS (EI): *m*/*z* (%) = 241 (75) [M^+], 196 (100). HRMS (EI): *m*/*z* calcd. for $C_{13}H_{11}N_3O_2$ [M^+] 241.0851; found 241.0855.

7-Phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidine (2g): Yellow solid (47.8 mg, 65%), m.p. 237–239 °C. IR (KBr): $\tilde{\nu}$ = 3427, 3053, 1499, 1458, 1336, 1191 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.82–8.78 (m, J = 2.0 Hz, 2 H), 8.06–8.04 (m, 2 H), 7.82 (dd, J = 8.5, 1.5 Hz, 1 H), 7.66 (d, J = 7.0 Hz, 2 H), 7.48 (t, J = 7.5 Hz, 2 H), 7.38 (t, J = 7.5 Hz, 1 H), 6.93 (dd, J = 7.0, 4.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 155.6, 151.0, 143.8, 141.1, 136.0, 133.4, 129.1, 127.6, 127.5, 126.7, 120.9, 108.9, 106.9 ppm. MS (EI): *m*/*z* (%) = 245 (100) [M^+], 218 (25). HRMS: *m*/*z* calcd. for $C_{16}H_{11}N_3$ [M^+] 245.0953; found 245.0956.

7-(*o*-Tolyl)benzo[4,5]imidazo[1,2-*a*]pyrimidine (2h): Yellow solid (58.3 mg, 75%), m.p. 263–265 °C. IR (KBr): $\tilde{\nu}$ = 3441, 3085, 1604, 1521, 1495 1190 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.84 (dd, J = 6.5, 2.0 Hz, 1 H), 8.78 (q, J = 2.0 Hz, 1 H), 8.02 (d, J = 8.5 Hz, 1 H), 7.85 (d, J = 1.0 Hz, 1 H), 7.54 (dd, J = 8.5, 1.5 Hz, 1 H), 7.30–7.26 (m, 4 H), 6.95 (dd, J = 7.0, 4.0 Hz, 1 H), 2.29 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 155.6, 150.8, 142.9, 141.6, 136.6, 135.7, 133.6, 130.5, 130.3, 128.6, 127.6, 126.8, 125.9, 119.9, 111.1, 106.9, 20.7 ppm. MS (EI): *m*/*z* (%) = 259 (100) [M^+], 258 (64). HRMS: *m*/*z* calcd. for $C_{17}H_{13}N_3$ [M^+] 259.1109; found 259.1114.

8-Methylbenzo[4,5]imidazo[1,2-*a*]pyrimidine (2i): Light yellow solid (42.3 mg, 77%), m.p. 199–200 °C. IR (KBr): $\tilde{\nu}$ = 3047, 1603, 1503, 1421, 1319, 792 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.77 (dd, J = 6.5, 2.0 Hz, 1 H), 8.74–8.73 (q, J = 2.0 Hz, 1 H), 7.77–7.75 (t, J = 4.0 Hz, 2 H), 7.21 (d, J = 8.5 Hz, 1 H), 6.89 (dd, J = 6.5, 4.0 Hz, 1 H), 2.55 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 155.2, 150.5, 144.2, 137.1, 133.5, 124.9, 124.1, 119.9, 110.5, 106.7, 22.2 ppm. MS (EI): *m*/*z* (%) = 183 (100) [M^+], 143 (82). HRMS (EI): *m*/*z* calcd. for $C_{11}H_9N_3$ [M^+] 183.0796; found 183.0795.

9-Methylbenzo[4,5]imidazo[1,2-*a*]pyrimidine (2j): Yellow solid (29.1 mg, 53%), m.p. 195–196 °C. IR (KBr): $\tilde{\nu}$ = 3067, 1619, 1597, 1500, 1377, 778 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.75 (dd, J = 4.0, 2.0 Hz, 1 H), 8.72 (dd, J = 6.5, 1.5 Hz, 1 H), 7.69 (d, J = 8.0 Hz, 1 H), 7.36 (d, J = 7.0 Hz, 1 H), 7.30 (t, J = 7.5 Hz, 1 H), 6.87 (dd, J = 7.0, 4.0 Hz, 1 H), 2.79 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 155.1, 150.1, 143.5, 133.3, 130.8, 126.6, 126.3, 122.1, 107.9, 106.5, 17.1 ppm. MS (EI): *m*/*z* (%) = 183 (23) [M^+], 154 (100). HRMS (EI): *m*/*z* calcd. for $C_{11}H_9N_3$ [M^+] 183.0796; found 183.0800.

9-Chlorobenzo[4,5]imidazo[1,2-*a*]pyrimidine (2k): Light yellow solid (47.5 mg, 78%), m.p. 262–264 °C. IR (KBr): $\tilde{\nu}$ = 3075, 1624, 1500, 1435, 1323, 1181 cm^{-1}. ^1H NMR ([D$_6$]DMSO, 500 MHz): δ = 9.55 (dd, J = 6.5, 1.5 Hz, 1 H), 8.91–8.90 (m, 1 H), 8.29 (d, J = 8.0 Hz, 1 H), 7.63 (d, J = 7.5 Hz, 1 H), 7.40 (t, J = 8.0 Hz, 1 H), 7.23 (dd, J = 6.5, 4.0 Hz, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 125 MHz): δ = 157.4, 150.3, 140.6, 136.4, 128.0, 125.6, 122.8, 121.8, 111.8, 107.6 ppm. MS (EI): *m*/*z* (%) = 205 (5) [M^+ (^{37}Cl)], 203 (14) [M^+ (^{35}Cl)], 154 (100). HRMS (EI): *m*/*z* calcd. for $C_{10}H_6N_3Cl$ [M^+] 203.0250; found 203.0247.

3-Bromobenzo[4,5]imidazo[1,2-*a*]pyrimidine (2l): Yellow solid (55.8 mg, 75%), m.p. 240–242 °C. IR (KBr): $\tilde{\nu}$ = 3049, 1618, 1512, 1479, 1293, 1064 cm^{-1}. ^1H NMR ([D$_6$]DMSO, 500 MHz): δ = 9.92 (d, J = 3.0 Hz, 1 H), 8.86 (d, J = 2.0 Hz, 1 H), 8.32 (d, J = 8.0 Hz,

1 H), 7.86 (d, J = 8.0 Hz, 1 H), 7.57–7.54 (m, 1 H), 7.44 (t, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 125 MHz): δ = 156.3, 148.1, 143.7, 135.9, 126.8, 126.4, 122.0, 119.4, 112.9, 101.3 ppm. MS (EI): m/z (%) = 249 (93) [M$^+$ (^{81}Br)], 247 (100) [M$^+$ (^{79}Br)], 168 (48). HRMS (EI): m/z calcd. for $C_{10}H_6N_3Br$ [M$^+$] 246.9745; found 246.9747.

3-Phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidine (2m): Yellow solid (65.7 mg, 90%), m.p. 230–232 °C. IR (KBr): $\tilde{\nu}$ = 3050, 1629, 1528, 1486, 1302, 1178 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 9.84 (d, J = 1.5 Hz, 1 H), 9.21 (d, J = 2.0 Hz, 1 H), 8.43 (d, J = 8.0 Hz, 1 H), 7.89–7.85 (m, 3 H), 7.55 (t, J = 7.5 Hz, 3 H), 7.46–7.42 (m, 2 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 125 MHz): δ = 155.7, 149.5, 144.0, 133.7, 132.5, 129.2, 128.1, 127.2, 126.7, 126.2, 121.5, 119.6, 119.3, 113.0 ppm. MS (EI): m/z (%) = 245 (100) [M$^+$], 218 (25). HRMS (EI): m/z calcd. for $C_{16}H_{11}N_3$ [M$^+$] 245.0953; found 245.0956.

Benzo[4,5]imidazo[1,2-*a*]pyridine (2n):[11] Brown solid (29.3 mg, 58%), m.p. 179–181 °C. IR (KBr): $\tilde{\nu}$ = 3016, 1641, 1502, 1354, 1258, 1142 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.40 (d, J = 7.0 Hz, 1 H), 7.92 (d, J = 8.0 Hz, 1 H), 7.85 (d, J = 8.0 Hz, 1 H), 7.67 (d, J = 9.0 Hz, 1 H), 7.53–7.49 (m, 1 H), 7.41–7.38 (m, 1 H), 7.36–7.33 (m, 1 H), 6.81 (td, J = 7.0, 1.0 Hz, 1 H) ppm. ^{13}C NMR (CDCl$_3$, 125 MHz): δ = 148.4, 144.3, 129.6, 128.7, 125.8, 125.3, 121.2, 119.9, 117.9, 110.5, 110.4 ppm. MS (EI): m/z (%) = 168 (13) [M$^+$], 144 (100).

Imidazo[1,2-*a*:4,5-*b*′]dipyridine (2o):[18] Brown solid (35.5 mg, 70%), m.p. 193–195 °C. IR (KBr): $\tilde{\nu}$ = 3047, 1643, 1479, 1347, 1248, 1154 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 8.76 (dd, J = 5.0, 1.5 Hz, 1 H), 8.50 (d, J = 6.5 Hz, 1 H), 8.21 (dd, J = 8.0, 1.5 Hz, 1 H), 7.75 (d, J = 9.0 Hz, 1 H), 7.50–7.47 (m, 1 H), 7.24 (dd, J = 8.0, 4.5 Hz, 1 H), 6.92 (td, J = 7.0, 1.5 Hz, 1 H) ppm. ^{13}C NMR (CDCl$_3$, 125 MHz): δ = 156.1, 149.5, 148.7, 130.9, 126.0, 121.2, 119.0, 118.3, 116.0, 111.5 ppm. MS (EI): m/z (%) = 169 (100) [M$^+$].

Benzo[4,5]imidazo[1,2-*a*]pyrazine (2p):[19] Brown solid (30.4 mg, 60%), m.p. 197–198 °C. IR (KBr): $\tilde{\nu}$ = 3054, 3019, 1490, 1342, 1271, 1005 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 9.31 (d, J = 1.5 Hz, 1 H), 8.36 (dd, J = 5.0, 2.0 Hz, 1 H), 8.06 (d, J = 8.5 Hz, 1 H), 7.99–7.96 (m, 2 H), 7.65–7.62 (m, 1 H), 7.52–7.49 (m, 1 H) ppm. ^{13}C NMR (CDCl$_3$, 125 MHz): δ = 145.7, 144.1, 142.1, 127.8, 127.5, 127.4, 123.5, 121.5, 118.0, 111.4 ppm. MS (ESI): m/z (%) = 170 [M + H].

Ethyl Imidazo[1,2-*a*]pyrimidine-3-carboxylate (4a):[6c] Yellow solid (48.8 mg, 85%), m.p. 121–123 °C. IR (KBr): $\tilde{\nu}$ = 3432, 2986, 1701, 1614, 1407, 1284 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 9.56 (dd, J = 7.0, 2.0 Hz, 1 H), 8.72 (dd, J = 4.0, 2.0 Hz, 1 H), 8.44 (s, 1 H), 7.13 (dd, J = 6.5, 4.0 Hz, 1 H), 4.41 (q, J = 7.0 Hz, 2 H), 1.41 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (CDCl$_3$, 125 MHz): δ = 160.4, 152.4, 150.8, 142.4, 135.6, 114.6, 110.6, 61.1, 14.5 ppm. MS (EI): m/z (%) = 191 (52) [M$^+$], 95 (100).

Methyl Imidazo[1,2-*a*]pyrimidine-3-carboxylate (4b): Light yellow solid (25.5 mg, 48%), m.p. 175–176 °C. IR (KBr): $\tilde{\nu}$ = 3367, 3105, 1705, 1616, 1529, 1286 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 9.55 (dd, J = 7.0, 2.0 Hz, 1 H), 8.73 (dd, J = 4.0, 2.0 Hz, 1 H), 8.44 (s, 1 H), 7.13 (dd, J = 6.5, 4.0 Hz, 1 H), 3.95 (s, 3 H) ppm. ^{13}C NMR (CDCl$_3$, 125 MHz): δ = 160.7, 152.5, 150.9, 142.8, 135.6, 114.3, 110.7, 51.9 ppm. MS (EI): m/z (%) = 177 (100) [M$^+$], 146 (83).

Benzyl Imidazo[1,2-*a*]pyrimidine-3-carboxylate (4c): Light yellow solid (50.9 mg, 67%), m.p. 135–137 °C. IR (KBr): $\tilde{\nu}$ = 3447, 3105, 1702, 1611, 1521, 1285 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 9.57 (d, J = 6.0 Hz, 1 H), 8.74 (d, J = 2.0 Hz, 1 H), 8.50 (s, 1 H), 7.45 (d, J = 7.5 Hz, 2 H), 7.41–7.36 (m, 3 H), 7.13 (dd, J = 6.5, 4.0 Hz, 1 H), 5.41 (s, 2 H) ppm. ^{13}C NMR (CDCl$_3$, 125 MHz): δ = 160.1, 152.5, 151.0, 142.9, 135.6, 135.5, 128.9, 128.7, 128.4, 114.3, 110.7, 66.6 ppm. MS (EI): m/z (%) = 253 (70) [M$^+$], 91 (100). HRMS (EI): m/z calcd. for $C_{14}H_{11}N_3O_2$ [M$^+$] 253.0851; found 253.0854.

1-(2-Methylimidazo[1,2-*a*]pyrimidin-3-yl)ethanone (4d):[20] Light yellow solid (27.3 mg, 52%), m.p. 115–117 °C. IR (KBr): $\tilde{\nu}$ = 3415, 3082, 1634, 1505, 1391, 1190 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 9.84 (dd, J = 7.0, 2.0 Hz, 1 H), 8.75 (dd, J = 4.5, 2.0 Hz, 1 H), 7.32 (dd, J = 7.0, 4.5 Hz, 1 H), 2.75 (s, 3 H), 2.59 (s, 3 H) ppm. ^{13}C NMR (CDCl$_3$, 125 MHz): δ = 188.4, 154.5, 153.2, 149.6, 136.7, 120.2, 110.9, 30.3, 18.3 ppm. MS (EI): m/z (%) = 175 (77) [M$^+$], 160 (100).

1-(2,5,7-Trimethylimidazo[1,2-*a*]pyrimidin-3-yl)ethanone (4e): Light yellow solid (28.0 mg, 46%), m.p. 116–118 °C. IR (KBr): $\tilde{\nu}$ = 3441, 2925, 1639, 1525, 1399, 1117 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 6.69 (s, 1 H), 2.74 (s, 3 H), 2.62 (s, 3 H), 2.58 (s, 3 H), 2.51 (s, 3 H) ppm. ^{13}C NMR (CDCl$_3$, 125 MHz): δ = 187.4, 163.2, 154.0, 151.7, 148.4, 122.7, 112.6, 30.5, 24.6, 22.5, 18.1 ppm. MS (EI): m/z (%) = 203 (47) [M$^+$], 188 (100).

(2-Methylimidazo[1,2-*a*]pyrimidin-3-yl)(phenyl)methanone (4f): Yellow solid (55.5 mg, 78%), m.p. 97–99 °C. IR (KBr): $\tilde{\nu}$ = 3441, 3062, 1612, 1525, 1392, 1210 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 9.73–9.71 (m, 1 H), 8.73 (d, J = 2.0 Hz, 1 H), 7.67–7.65 (m, 2 H), 7.61–7.58 (m, 1 H), 7.53–7.49 (m, 2 H), 7.13–7.10 (m, 1 H), 2.24 (s, 3 H) ppm. ^{13}C NMR (CDCl$_3$, 125 MHz): δ = 187.3, 155.1, 153.5, 150.2, 139.7, 136.3, 132.3, 128.8, 128.5, 119.8, 110.7, 17.7 ppm. MS (EI): m/z (%) = 237 (44) [M$^+$], 105 (100). HRMS (EI): m/z calcd. for $C_{14}H_{11}N_3O$ [M$^+$] 237.0902; found 237.0901.

(2-Ethylimidazo[1,2-*a*]pyrimidin-3-yl)(phenyl)methanone (4g):[21] Light yellow solid (67.1 mg, 89%), m.p. 137–138 °C. IR (KBr): $\tilde{\nu}$ = 3443, 3134, 1616, 1523, 1384, 1207 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 9.68 (d, J = 7.0 Hz, 1 H), 8.73 (t, J = 2.0 Hz, 1 H), 7.68 (d, J = 7.5 Hz, 2 H), 7.60 (t, J = 7.5 Hz, 1 H), 7.51 (t, J = 7.5 Hz, 2 H), 7.10 (q, J = 4.5 Hz, 1 H), 2.51 (q, J = 7.0 Hz, 2 H), 1.21 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (CDCl$_3$, 125 MHz): δ = 187.4, 160.2, 153.4, 150.5, 139.9, 136.3, 132.4, 128.8, 128.5, 119.1, 110.7, 23.7, 13.5 ppm. MS (EI): m/z (%) = 251 (87) [M$^+$], 250 (100).

Phenyl(2-propylimidazo[1,2-*a*]pyrimidin-3-yl)methanone (4h): Light yellow solid (63.7 mg, 80%), m.p. 136–137 °C. IR (KBr): $\tilde{\nu}$ = 3444, 2963, 1617, 1521, 1385, 1202 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 9.68 (dd, J = 7.0, 2.0 Hz, 1 H), 8.73 (q, J = 2.0 Hz, 1 H), 7.68 (d, J = 7.5 Hz, 2 H), 7.61 (t, J = 7.5 Hz, 1 H), 7.51 (t, J = 7.5 Hz, 2 H), 7.12–7.09 (m, 1 H), 2.46 (t, J = 7.5 Hz, 2 H), 1.72–1.64 (m, 2 H), 0.72 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (CDCl$_3$, 125 MHz): δ = 187.5, 159.1, 153.4, 150.4, 139.9, 136.3, 132.4, 128.8, 128.4, 119.5, 110.6, 32.2, 22.9, 14.0 ppm. MS (EI): m/z (%) = 265 (9) [M$^+$], 236 (100). $C_{16}H_{15}N_3O$ (265.31): calcd. C 72.43, H 5.70, N 15.84; found C 72.40, H 5.59, N 15.47.

(4-Methoxyphenyl)(2-methylimidazo[1,2-*a*]pyrimidin-3-yl)methanone (4i): Light yellow solid (65.0 mg, 81%), m.p. 119–121 °C. IR (KBr): $\tilde{\nu}$ = 3441, 3063, 1613, 1598, 1387, 1262 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 9.57 (d, J = 6.5 Hz, 1 H), 8.70 (q, J = 2.0 Hz, 1 H), 7.70 (AA′ of AA′BB′, J = 9.0 Hz, 2 H), 7.08–7.06 (m, 1 H), 7.00 (BB′ of AA′BB′, J = 9.0 Hz, 2 H), 3.89 (s, 3 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (CDCl$_3$, 125 MHz): δ = 186.1, 163.4, 153.8, 153.1, 150.1, 136.0, 131.9, 131.3, 119.9, 114.1, 110.4, 55.7, 17.8 ppm. MS (EI): m/z (%) = 267 [M$^+$], 135 (100). HRMS (EI): m/z calcd. for $C_{15}H_{13}N_3O_2$ [M$^+$] 267.1008; found 267.1004.

Phenyl(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methanone (4j):[22] Light yellow solid (76.1 mg, 85%), m.p. 130–132 °C. IR (KBr): $\tilde{\nu}$ = 3423,

3062, 1600, 1574, 1492, 1222 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 9.53 (d, J = 6.5 Hz, 1 H), 7.81 (d, J = 9.0 Hz, 1 H), 7.54–7.49 (m, 3 H), 7.32–7.30 (m, 2 H), 7.24 (t, J = 7.5 Hz, 1 H), 7.12–7.06 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 187.4, 154.8, 147.3, 138.6, 133.8, 131.9, 130.3, 129.6, 129.4, 128.4, 128.3, 127.8, 120.0, 117.4, 114.8 ppm. MS (EI): m/z (%) = 298 (100) [M^+], 297 (73).

2-Methyl-1*H*-cyclopenta[4,5]imidazo[1,2-*a*]pyridin-3(2*H*)-one (4k): Light yellow solid (29.1 mg, 52%), m.p. 212–214 °C. IR (KBr): $\tilde{\nu}$ = 3453, 3075, 1694, 1511, 1444, 1106 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.01 (d, J = 6.5 Hz, 1 H), 7.66 (d, J = 9.5 Hz, 1 H), 7.29 (t, J = 7.0 Hz, 1 H), 6.91 (t, J = 6.5 Hz, 1 H), 3.44 (q, J = 6.5 Hz, 1 H), 3.17 (t, J = 5.5 Hz, 1 H), 2.76 (d, J = 16.5 Hz, 1 H), 1.41 (d, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 198.3, 151.9, 148.4, 145.9, 127.3, 124.6, 120.2, 113.6, 47.4, 27.1, 17.1 ppm. MS (EI): m/z (%) = 186 (76) [M^+], 157 (100). HRMS (EI): m/z calcd. for $C_{11}H_{10}N_2O_1$ [M^+] 186.0793; found 186.0794.

Supporting Information (see footnote on the first page of this article): Experimental details, spectroscopic characterization data, copies of the ^1H NMR and ^{13}C NMR spectra for all compounds are given in the Supporting Information.

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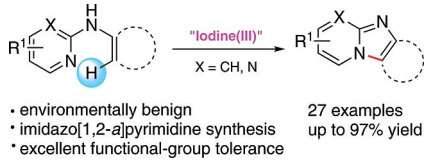
Imidazo[1,2-*a*]-type fused heterocycles are prevalent structural motifs in pharmaceutically and biologically active compounds. In this paper, an efficient and mild synthesis of imidazo[1,2-*a*]pyrimidine skeletons was developed from readily available pyrimidyl arylamines or enamines through a hypervalent iodine-promoted intramolecular C–H bond cycloamination reaction.



Nitrogen Heterocycles

Keywords: Synthetic methods / Nitrogen heterocycles / C–H functionalization / Amination / Iodine

