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Natural α-Amino Acids Applied in the Synthesis of Imidazo[1,5-*a*]N-heterocycles under Mild Conditions

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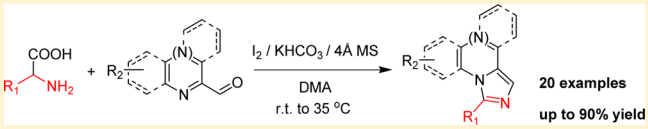
Supporting Information

ABSTRACT: A facile iodine-mediated decarboxylative cyclization from α-amino acids and N-heterocyclic carbaldehydes was developed. By virtue of this method, a series of imidazo[1,5-*a*]N-heterocycles can be synthesized efficiently under mild conditions. A tentative reaction mechanism was proposed based on the experimental results and previous reports.



INTRODUCTION

As an important class of heteroaromatics, imidazo[1,5-*a*]N-heterocycles have many applications for their potential photophysical and biological activities.[1] For example, the imidazo[1,5-*a*]pyridine skeleton (2-azaindolizines) has potential applications in organic light-emitting diodes (OLEDs) and organic thin-layer field effect transistors (FETs).[2] Meanwhile, this structure could also be considered as a precursor for N-heterocyclic carbene.[3] Furthermore, imidazo[1,5-*a*]quinoline is an important moiety of NK1 receptor ligands,[4a] and imidazo-[1,5-*a*]quinoxaline is the critical skeleton for inhibitors targeting phosphodiesterase 10A.[4b] Despite the significance in the above-mentioned areas, only a few synthetic routes are available for these compounds so far.[5,6] The process of these reported routes mainly relied on traditional Vilsmeier-type cyclizations of *N*-2-pyridylmethyl amides. Therefore, alternative synthetic approaches for imidazo[1,5-*a*]N-heterocycles are desired.

Azomethine ylides as active reactants have been widely used in organic synthesis,[7] especially in pericyclic reactions for heterocycles.[8] α-Amino acids have long been recognized as precursors for active azomethine ylides under some specific conditions.[9] Recently, a series of cascade decarboxylative reactions involving azomethine ylides have been developed by Seidel,[7e,9e] Li,[9c,g] and Dang/Bai[9b] to construct C−C and C−N bonds (Figure 1). On the basis of a similar principle, our group also developed some decarboxylative cyclization reactions with primary α-amino acids to prepare pyridines and quinazolines.[10] However, transition metals,[9c,f,g] high temperatures,[9a−i] and peroxides[9c,d] were usually required to enable the decarboxylative activation for the generation of azomethine ylides. Therefore, the development of facile and mild conditions for this kind of reaction is still challenging and bears great significance. As an extension of our research on the decarboxylative reaction of primary α-amino acids (Figure 2), herein we report new and efficient methods for the synthesis of imidazo[1,5-*a*]N-heterocycles.

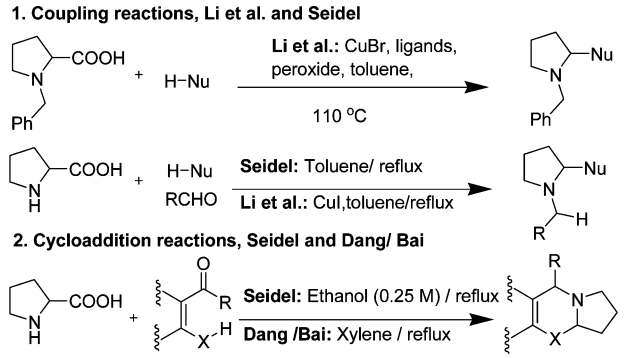


Figure 1. Representative work showing decarboxylative reactions of α-amino acids involving in situ-generated azomethine ylides.

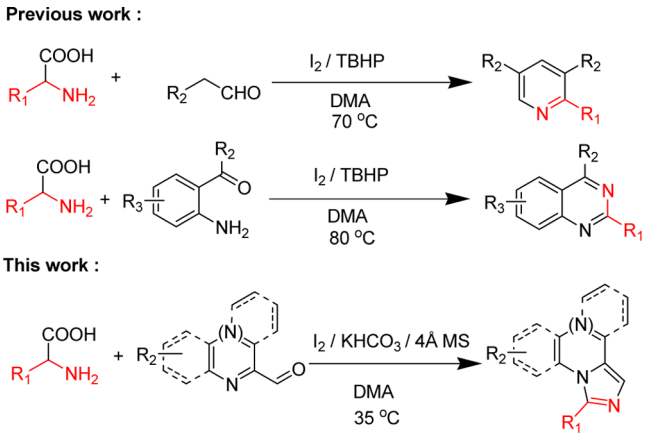


Figure 2. Our group's work: primary α-amino acids participated in decarboxylative cyclizations involving in situ-generated azomethine ylides.

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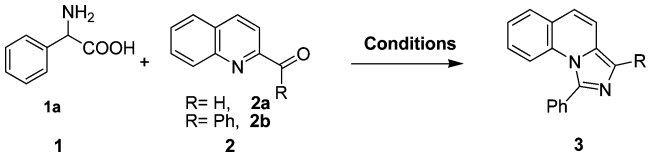
RESULTS AND DISCUSSION

Initially, we employed quinoline-2-carbaldehyde **1a** and phenylglycine **2a** as model substrates, 20 mol % iodine as catalyst, and DMA as solvent, and the mixture was stirred at room temperature for 3 h. The desired products 1-phenylimidazo[1,5-*a*]quinoline **3a** was obtained in 17% yield (Table 1, entry 1). In the subsequent optimization, it was found

Table 1. Optimization of the Reaction Conditions[a]



entry	2	catalyst	additive[b]	temperature	yield (%)[c]
1	**2a**	20 mol % I_2	–	rt	17
2	**2a**	20 mol % I_2	4 Å MS	rt	32
3[d]	**2a**	20 mol % Ag_2O	4 Å MS	rt	trace
4[d]	**2a**	20 mol % $CuBr_2$	4 Å MS	rt	trace
5[d]	**2a**	20 mol % $FeCl_3$	4 Å MS	rt	trace
6	**2a**	50 mol % I_2	4 Å MS	rt	43
7	**2a**	100 mol % I_2	4 Å MS	rt	58
8	**2a**	100 mol % I_2	4 Å MS	35 °C	63
9	**2a**	100 mol % I_2	4 Å MS/ $NaHCO_3$	35 °C	75
10	**2a**	100 mol % I_2	4 Å MS/$KHCO_3$	35 °C	81
11	**2a**	100 mol % I_2	4 Å MS/K_2CO_3	35 °C	71
12	**2a**	100 mol % I_2	4 Å MS/Et_3N	35 °C	63
13	**2a**	100 mol % I_2	4 Å MS/$KHCO_3$	50 °C	73
14	**2a**	120 mol % I_2	4 Å MS/$KHCO_3$	35 °C	76
15	**2a**	150 mol % I_2	4 Å MS/$KHCO_3$	35 °C	68
16	**2b**	100 mol % I_2	4 Å MS/$KHCO_3$	35 °C	n.d.
17	**2b**	100 mol % I_2	4 Å MS/KHCO3	80 °C	n.d.
18	**2b**	50 mol % I_2	4 Å MS/TBHP	80 °C	n.d

[a]A mixture of L-Phg (0.22 mmol, 1.1 equiv), quinoline-2-carbaldehyde (0.2 mmol, 1.0 equiv), 1.5 mL of DMA (*N*,*N*-dimethylacetamide), and additives was stirred with different catalysts under air for 3 h. [b]100 mg of 4 Å MS, 2.0 equiv of base or TBHP. [c]n. d. = not detected. [d]Reaction time was 5 h.

that 4 Å MS (molecular sieve) could improve the yield (Table 1, entry 2). Then different potential catalysts were examined. As shown in Table 1, iodine showed special capability to promote the reaction, while other metal salts and a metal oxide had no catalytic activity in this reaction (Table 1, entries 2–5). Cupric bromide, ferric trichloride, and silver oxide, which have been frequently employed in decarboxylative reactions, had no catalytic activity in this reaction (Table 1, entries 3–5). To further improve the yield, different iodine loadings were evaluated. With an increase in the iodine loading, the reaction yield was enhanced (Table 1, entries 2, 6, and 7). When the loading of iodine was increased to 100 mol %, the reaction yield was improved to 58% (Table 1, entry 7). However, yields decreased when more than 1 equiv of iodine was employed (Table 1, entries 14 and 15). Also, the temperature had an influence on the reaction. When the temperature was raised to 35 °C, the reaction yield was improved to 63% (Table 1, entry 8). Further increase in the temperature to 50 °C decreased the yield to 73% with unknown side reactions (Table 1, entry 13). Experimental results indicated that base could facilitate this reaction (Table 1, entries 8 and 9). Among the bases examined, $KHCO_3$ was the best, which gave the desired product in 81% yield (Table 1, entry 10). We also employed phenyl(quinolin-2-yl)methanone **2b** as the reaction substrate for this decarboxylative reaction (Table 1, entries 16–18). However, no desired product was observed under the selected conditions. Finally, the optimized reaction conditions were obtained as described (Table 1, entry 10): 1.0 equiv of aldehyde **2a**, 1.1 equiv of α-amino acid **1a**, 1.0 equiv of iodine, 2.0 equiv of $KHCO_3$, and 100 mg of 4 Å MS in 1.5 mL of DMA at 35 °C for 3 h.

With the optimized conditions in hand, the substrate scope was examined (Table 2). Results indicated that various aliphatic α-amino acids could be successfully applied in this reaction, such as Ala (alanine), Glu-5-OMe (glutamic acid 5-methyl ester), Ile (isoleucine), Leu (leucine), Nor-Leu (nor-leucine), Val (valine), Nor-Val (nor-valine), Met (methionine), and Phe (phenylalanine) (Table 2, entries 2–9). Moreover, Thr (threonine) and Ser (serine), which contain active hydrogens on the side chains, could also afford the desired products in satisfactory yields (Table 2, entries 11 and 12). Aromatic α-amino acids gave better results than aliphatic α-amino acids in the reactions (Table 2, entries 1–10, 15, and 16), probably because aromatic rings could stabilize the reaction intermediate via π-conjugation. Furthermore, the steric hindrance from the α-amino acid side chains had little influence on the reaction. For instance, **1c** and **1f**, bearing large substitutions at the β-positions, also gave the corresponding products in good yields although a prolonged reaction time was needed (Table 2, entries 3 and 5). On the other hand, different N-heterocyclic carbaldehydes, such as quinoline-2-carbaldehydes, picolinaldehydes, quinoxaline-2-carbaldehyde, and isoquinoline-1-carbaldehyde, were also examined in this reaction. It was found that all these N-heterocyclic carbaldehydes provided the corresponding products in good yields (Table 2, entries 13–20). Furthermore, a weak electronic effect from the different N-heterocyclic carbaldehydes was observed. In comparison with the electron-withdrawing substitution, the electron-donating substitution on the N-heterocyclic carbaldehydes favored this reaction to some extent (Table 2, entries 13 and 14, 17 and 18). Compared to the previous reports,[9,10] this decarboxylative cyclization reaction had a much wider substrate scope for α-amino acids, and many potential optical materials with various photophysical properties could be obtained by using this method.

To investigate the reaction mechanism, radical trapping experiments and an oxygen-free experiment were performed as control experiments. Two equivalents of radical scavenger was added to the reaction mixture, and little influence on the reaction yield was observed (Figure 3 A), which implied that the decarboxylative pathway did not involve a radical pathway. As a result, this process is different from that of our previous work.[10b] In that case, the decarboxylation process proved to be a radical reaction. Oxygen-free experiment indicated that this cascade reaction did not require additional oxidant for the final aromatization (Figure 3 B).

Based on the results above and the previous reports,[9] a plausible mechanism for the model reaction was proposed (Scheme 1). The reaction starts from the condensation of phenylglycine **1a** with quinoline-2-carbaldehyde **2a** to form imine **I**, followed by the N-iodination to give intermediate **II**. Subsequently, the intermediate **II** experiences a $KHCO_3$-promoted decarboxylative pathway to generate intermediate **IIIa**. **IIIa** can transform to **IIIb** by tautomerization. And **IIIb** can be easily cyclized through an intramolecular nucleophilic

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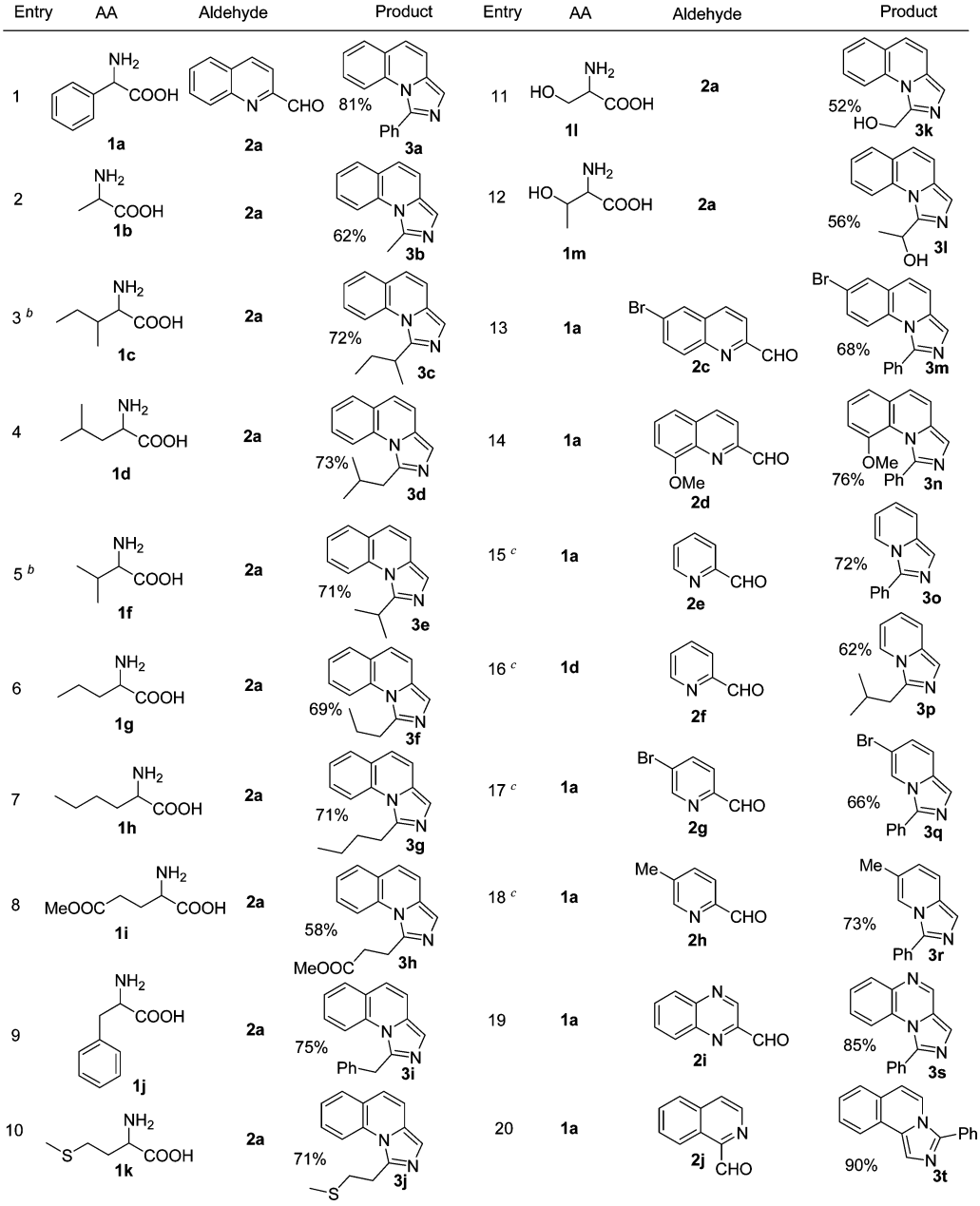
Table 2. Decarboxylative Cyclization of Different α-Amino Acids with N-Heterocyclic Carbaldehydes[a]



[a]Reaction scale and conditions: 0.2 mmol N-heterocyclic carbaldehydes, 0.22 mmol of α-amino acids, 0.2 mmol of I_2, 0.4 mmol of $KHCO_3$, 1.5 mL of DMA, and 100 mg of powder 4 Å MS. Stirred at 35 °C for 3 h. [b]Reaction time 4 h. [c]Room temperature for 4 h.

addition to give **IV**. Finally, **IV** loses a hydrogen iodide to give the final product **3a**.

CONCLUSION

In summary, we have developed a facile decarboxylative cyclization to construct imidazo[1,5-*a*]N-heterocycles by virtue of the azomethine ylides generated in situ. With readily available starting materials, a variety of imidazo[1,5-*a*]N-heterocycles containing α-amino acid moieties can be prepared efficiently. Compared to previous reports, the substrate scope of the primary α-amino acid was largely extended. In particular, no metal was required in the reaction, avoiding a metal residue in the products. Moreover, the compounds constructed by this methodology bear great research significance for their potentially photophysical and biological activities.

EXPERIMENTAL SECTION

Typical Procedure: The Synthesis of 3a. Iodine (51.4 mg, 0.2 mmol) was dissolved in 1.5 mL of DMA, and powdered 4 Å MS (150 mg), potassium bicarbonate (40 mg, 0.4 mmol), L-Phg (33.2 mg, 0.22 mmol), and quinoline-2-carbaldehyde (31.4 mg, 0.2 mmol) were added. The system was stirred under air at 35 °C, and the reaction process was monitored by TLC. After 3 h, the system was cooled to room temperature and extracted with ethyl acetate (3 × 20 mL), and then the organic layer was washed with brine (2 × 10 mL) and dried with anhydrous Na_2SO_4. Subsequently, the solvent was removed and the product was purified by flash column chromatography (petroleum ether:ethyl acetate = 10:1) to give 1-phenylimidazo[1,5-*a*]quinoline (39.5 mg, 81%) as a light yellow solid.

Substrate Preparation. *6-Bromoquinoline-2-carbaldehyde (**2c**).* Prepared according to a similar procedure[11] from 6-bromo-2-methylquinoline (302 mg, 1.37 mmol) and purified by column

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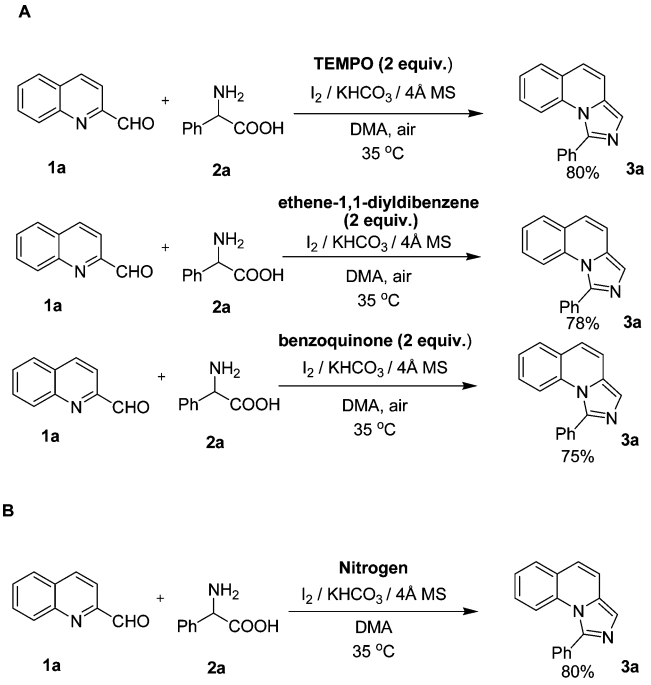
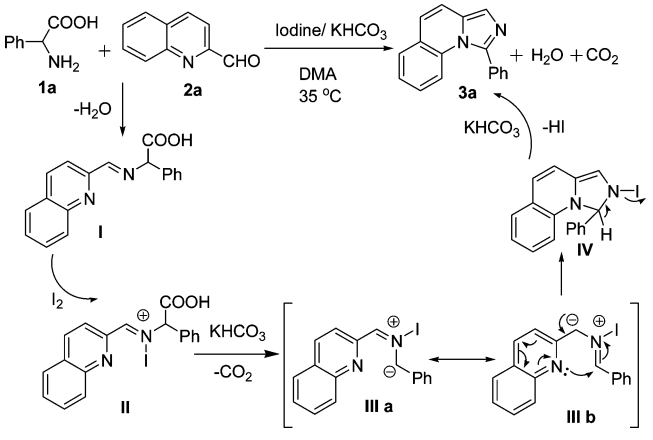


Figure 3. Radical trapping experiments (A) and oxygen-free experiment (B).

Scheme 1. Proposed Mechanism for the Decarboxylative Cyclization



chromatography on silica gel with ethyl acetate:petroleum ether (1:20 v/v) as eluent to give the product as yellow solid (231 mg, 72%), mp = 143−145 °C. ^{1}H NMR ($CDCl_3$): δ 10.20 (s, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.13−8.04 (m, 3H), 7.91−7.88 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 193.4, 152.9, 146.6, 136.4, 134.2, 132.1, 131.1, 130.1, 123.7, 118.3. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{10}H_7BrNO$ 235.9706, found 235.9703.

*8-Methoxyquinoline-2-carbaldehyde (**2d**).* Prepared according to a procedure[11] from 6-bromo-2-methylquinoline (1.38 g, 8 mmol) and purified by column chromatography on silica gel with ethyl acetate:petroleum ether (1:5 v/v) as eluent to give the product as yellow solid (1.17 g, 78%), mp = 101−103 °C. ^{1}H NMR ($CDCl_3$): δ 10.33 (s, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.65−7.61 (m, 1H), 7.50−7.48 (m, 1H), 7.17 (d, J = 7.6 Hz, 1H), 4.17 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 193.7, 156.2, 151.6, 140.0, 137.4, 131.4, 129.9, 119.7, 118.0, 56.4. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{11}H_{10}NO_2$ 188.0706, found 188.0702.

*5-Bromopicolinaldehyde (**2g**).* Prepared according to a procedure[12] from 2,5-dibromopyridine (1.18 g, 5 mmol), and the pure product was obtained by column chromatography with ethyl acetate:petroleum ether (15:1 v/v) as eluent to give the product as yellow solid (342 mg, 37%), mp = 93−95 °C. ^{1}H NMR ($CDCl_3$): δ 10.04 (s, 1H), 8.86 (d, J = 1.6 Hz, 1H), 8.04−8.01 (m, 1H), 7.87−7.85 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 191.3, 150.6, 150.3, 138.9, 125.2, 121.7. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for C_6H_5BrNO 185.9549, found 185.9547.

*5-Methylpicolinaldehyde (**2h**).* Prepared according to a procedure[12] from 2-bromo-5-methylpyridine (850 mg, 5 mmol), and the pure product was obtained by column chromatography with ethyl acetate:petroleum ether (5:1 v/v) as eluent to give the product as yellow solid (248 mg, 41%), mp = 37−39 °C. ^{1}H NMR ($CDCl_3$): δ 10.05 (s, 1H), 8.62−8.61 (m, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.69−7.66 (m, 1H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$) 193.2, 150.84, 150.81, 138.7, 137.4, 121.4, 18.8. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for C_7H_8NO 122.0600, found 122.0593.

*Quinoxaline-2-carbaldehyde (**2i**).* 2-Methylquinoxaline (432 mg, 3 mmol) and selenium dioxide (433 mg, 3.9 mmol) were heated at 80 °C in a mixture of dioxane and H_2O (5:1 v/v, 12 mL) for 8 h, and the system was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated, and purified by column chromatography with acetate:petroleum ether (1:10 v/v) as eluent to give the product as a yellow solid (270 mg, 57%), mp = 109−111 °C. ^{1}H NMR ($CDCl_3$):[13] δ 10.29 (s, 1H), 9.43 (s, 1H), 8.27−8.20 (m, 2H), 7.97−7.89 (m, 2H). ^{13}C NMR ($CDCl_3$) 192.7, 146.0, 144.5, 142.5, 142.0, 132.9, 131.2, 130.5, 129.7. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_9H_7N_2O$ 159.0553, found 159.0549.

Analytical and Spectral Data for the Products. *1-Phenylimidazo[1,5-a]quinoline (**3a**).* Synthesized according to the typical procedure and purified by column chromatography (petroleum ether:ethyl acetate = 5:1) to give a light yellow solid (39.5 mg, 81%), mp = 113−115 °C. ^{1}H NMR ($CDCl_3$) δ 7.66−7.61 (m, 2H), 7.61−7.58 (m, 2H), 7.53−7.49 (m, 4H), 7.33−7.27 (m, 2H), 7.18−7.13 (m, 1H), 7.01−6.69 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 142.5, 133.9, 132.4, 130.6, 129.7, 129.3, 128.8, 128.7, 127.4, 125.7, 125.2, 122.5, 121.5, 117.5, 117.2. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{17}H_{13}N_2$ 245.1073, found 245.1076. IR (cm^{-1}) ν 2956, 2920, 1454, 1371, 812, 754.

*1-Methylimidazo[1,5-a]quinoline (**3b**).* Synthesized according to typical procedure and purified by column chromatography (petroleum ether:ethyl acetate = 5:1) to give a light yellow oil (22.5 mg, 62%). ^{1}H NMR ($CDCl_3$) δ 8.18−8.16 (d, J = 8.4 Hz, 1H), 7.61−7.59 (m, 1H), 7.50−7.45 (m, 1H), 7.38−7.34 (m, 1H), 7.30 (s, 1H), 7.23−7.20 (d, J = 9.6 Hz, 1H), 6.90−6.88 (d, J = 8.8 Hz, 1H), 3.05 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 139.1, 132.4, 129.4, 127.6, 126.8, 124.8, 123.9, 119.6, 119.6, 116.4, 115.2, 18.6. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{12}H_{11}N_2$ 183.0917, found 183.0916. IR (cm^{-1}) ν 2954, 2923, 1453, 1385, 808, 754.

*1-sec-Butylimidazo[1,5-a]quinoline (**3c**).* Synthesized according to the typical procedure but extending the reaction time to 4 h and purified by column chromatography (petroleum ether:ethyl acetate = 8:1) to give a light yellow oil (32.3 mg, 72%). ^{1}H NMR ($CDCl_3$) δ 8.14−8.12 (d, J = 8.4 Hz, 1H), 7.62−7.60 (m, 1H), 7.52−7.48 (m, 1H), 7.38−7.34 (m, 2H), 7.25−7.22 (d, J = 9.2 Hz, 1H), 3.62 −3.57 (m, 1H), 2.21−2.14 (m, 1H), 1.84−1.77 (m, 1H), 1.54 (d, J = 6.0 Hz, 3H), 1.04 (t, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 148.8, 133.3, 130.2, 128.8, 127.7, 126.2, 124.8, 120.9, 120.6, 117.6, 117.0, 36.8, 28.6, 19.0, 12.0. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{15}H_{17}N_2$ 225.1386, found 225.1382. IR (cm^{-1}) ν 2964, 2928, 1473, 1453, 809, 753.

*1-Isobutylimidazo[1,5-a]quinoline (**3d**).* Synthesized according to the typical procedure and purified by column chromatography (petroleum ether:ethyl acetate = 5:1) to give a light yellow oil (32.7 mg, 73%). ^{1}H NMR ($CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 1H), 7.62−7.60 (m, 1H), 7.52−7.48 (m, 1H), 7.38−7.34 (m, 2H), 7.25 (d, J = 9.6 Hz, 1H), 6.91 (d, J = 9.6 Hz, 1H), 3.25 (d, J = 6.8 Hz, 2H), 2.42−2.39 (m, 1H), 1.09 (d, J = 6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 143.5, 133.2, 130.4, 128.7, 127.7, 126.0, 124.9, 120.8, 120.6, 117.5, 116.6, 41.2, 26.6, 22.7. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{15}H_{17}N_2$ 225.1386, found 225.1383 IR (cm^{-1}) ν 2955, 2867, 1471, 1383, 809, 753.

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*1-Isopropylimidazo[1,5-a]quinoline (**3e**).* Synthesized according to the typical procedure but extending the reaction time to 4 h and purified by column chromatography (petroleum ether:ethyl acetate = 5:1) to give a light yellow oil (29.8 mg, 71%). ^{1}H NMR ($CDCl_3$) δ 8.17 (d, J = 8.4 Hz, 1H), 7.62−7.60 (m, 1H), 7.52−7.48 (m, 1H), 7.38−7.34 (m, 4H), 7.25 (d, J = 9.2 Hz, 1H), 6.91 (d, J = 9.2 Hz, 1H), 3.84−3.79 (m, 1H), 1.57 (d, J = 6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 149.5, 133.2, 130.3, 128.8, 127.8, 126.1, 124.8, 120.8, 120.6, 117.6, 117.0, 30.1, 21.7. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{14}H_{15}N_2$ 211.1230, found 211.1229. IR (cm^{-1}) ν 2968, 2926, 1475, 1453, 809, 754.

*1-Propylimidazo[1,5-a]quinoline (**3f**).* Synthesized according to the typical procedure and purified by column chromatography (petroleum ether:ethyl acetate = 5:1) to give a light yellow oil (28.9 mg, 69%). ^{1}H NMR ($CDCl_3$) δ 8.13 (d, J = 8.4 Hz, 1H), 7.62−7.60 (m, 1H), 7.52−7.48 (m, 1H), 7.38−7.34 (m, 2H), 7.24 (d, J = 9.2 Hz, 1H), 6.91 (d, J = 9.2 Hz, 1H), 3.35−3.31 (m, 2H), 2.07−1.98 (m, 2H), 1.15−1.12 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 144.1, 133.3, 130.3, 128.7, 127.8, 125.9, 124.8, 120.8, 120.6, 117.5, 116.6, 34.5, 20.6, 14.1. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{14}H_{15}N_2$ 211.1230, found 211.1232. IR (cm^{-1}) ν 2959, 2870, 1453, 1389, 807, 753.

*1-Butylimidazo[1,5-a]quinoline (**3g**).* Synthesized according to the typical procedure and purified by column chromatography (petroleum ether:ethyl acetate = 5:1) to give a light yellow oil (31.8 mg, 71%). ^{1}H NMR ($CDCl_3$) δ 8.13 (d, J = 8.4 Hz, 1H), 7.62−7.60 (m, 1H), 7.52−7.48 (m, 1H), 7.38−7.34 (m, 2H), 7.24 (d, J = 9.2 Hz, 1H), 6.91 (d, J = 9.2 Hz, 1H), 3.37−3.33 (m, 2H), 2.02−1.94 (m, 2H), 1.59−1.53 (m, 2H), 1.04−1.00 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 144.3, 133.3, 130.3, 128.7, 127.8, 125.9, 124.9, 120.7, 120.6, 117.5, 116.6, 32.2, 29.4, 22.7, 14.0. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{15}H_{17}N_2$ 225.1386, found 225.1382. IR (cm^{-1}) ν 2955, 2869, 1453, 1389, 808, 753.

*Methyl 3- (Imidazo[1,5-a]quinolin-1-yl)propanoate (**3h**).* Synthesized according to the typical procedure and purified by column chromatography (petroleum ether:ethyl acetate = 5:1) to give a light yellow solid (29.5 mg, 58%), mp = 101−103 °C. ^{1}H NMR ($CDCl_3$) δ 8.19 (d, J = 8.4 Hz, 1H), 7.63−7.61 (m, 1H), 7.53−7.49 (m, 1H), 7.39−7.33 (m, 2H), 7.24 (d, J = 9.2 Hz, 1H), 6.93 (d, J = 9.2 Hz, 1H), 3.75 (s, 3H), 3.68−3.65 (m, 2H), 3.15−3.11 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 173.5, 142.1, 133.2, 130.7, 128.7, 127.9, 125.9, 125.0, 120.9, 120.8, 117.4, 116.6, 52.0, 31.4, 27.8. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{15}H_{15}N_2O_2$ 255.1128, found 255.1127. IR (cm^{-1}) ν 2950, 2923, 1737, 1452, 1168, 809, 756.

*1-Benzylimidazo[1,5-a]quinoline (**3i**).* Synthesized according to the typical procedure and purified by column chromatography (petroleum ether:ethyl acetate = 8:1) to give a light yellow solid (38.7 mg, 75%), mp = 95−97 °C. ^{1}H NMR ($CDCl_3$) δ 7.98−7.96 (m, 1H), 7.57−7.55 (m, 1H), 7.32−7.24 (m, 5H), 7.21−7.13 (m, 3H), 6.94 (d, J = 9.2 Hz, 1H), 4.80 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 141.5, 137.0, 132.6, 130.8, 128.9, 128.5, 128.3, 127.8, 126.8, 125.7, 125.0, 121.4, 121.0, 117.3, 116.9, 37.9. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{18}H_{15}N_2$ 259.1230, found 259.1227. IR (cm^{-1}) ν 2923, 2851, 1453, 1386, 811, 721.

*1-(2-(Methylthio)ethyl)imidazo[1,5-a]quinoline (**3j**).* Synthesized according to the typical procedure and purified by column chromatography (petroleum ether:ethyl acetate = 5:1) to give a light yellow solid (34.4 mg, 71%), mp = 71−73 °C. ^{1}H NMR ($CDCl_3$) δ 8.11 (d, J = 8.4 Hz, 1H), 7.64−7.62 (m, 1H), 7.52−7.50 (m, 1H), 7.40−7.35 (m, 2H), 7.25 (d, J = 9.2 Hz, 1H), 6.94 (d, J = 9.2 Hz, 1H), 3.67−3.63 (m, 2H), 3.19−3.15 (m, 2H), 2.24 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 142.1, 133.0, 130.5, 128.8, 128.0, 125.9, 125.1, 120.9, 117.4, 116.4, 32.9, 31.5, 16.0. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{14}H_{15}N_2S$ 243.0950, found 243.0946. IR (cm^{-1}) ν 2960, 2918, 1474, 1389, 808, 754.

*Imidazo[1,5-a]quinolin-1-ylmethanol (**3k**).* Synthesized according to the typical procedure and purified by column chromatography (petroleum ether:ethyl acetate = 2:1) to give a light yellow solid (20.6 mg, 52%), mp = 113−115 °C. ^{1}H NMR ($CDCl_3$) δ 8.44 (d, J = 8.4 Hz, 1H), 7.68−7.66 (m, 1H), 7.63−7.59 (m, 1H), 7.46−7.42 (m, 1H), 7.31 (s, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 9.6 Hz, 1H), 5.26 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 142.5, 132.6, 131.1, 128.8, 128.6, 125.6, 125.5, 122.0, 120.4, 117.9, 117.0, 59.2. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{12}H_{11}N_2O$ 199.0866, found 199.0863. IR (cm^{-1}) ν 3310, 2957, 2925, 1452, 811, 733.

*1-(Imidazo[1,5-a]quinolin-1-yl)ethanol (**3l**).* Synthesized according to the typical procedure and purified by column chromatography (petroleum ether:ethyl acetate = 2:1) to give a light yellow solid (23.7 mg, 56%), mp = 109−111 °C. ^{1}H NMR ($CDCl_3$) δ 8.46 (d, J = 8.4 Hz, 1H), 7.64−7.62 (m, 1H), 7.58−7.54 (m, 1H), 7.43−7.41 (m, 1H), 7.26 (s, 1H), 7.21 (d, J = 9.6 Hz, 1H), 6.99 (d, J = 9.2H, 1H), 5.54−5.49 (m, 1H), 3.23 (s, 1H), 1.87 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 145.6, 132.6, 131.0, 128.6, 128.5, 125.7, 125.4, 121.7, 120.2, 118.4, 117.0, 64.6, 22.6. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{13}H_{13}N_2O$ 213.1022, found 213.1020. IR (cm^{-1}) ν 3207, 2957, 2869, 1453, 1370, 1088, 811, 756.

*7-Bromo-1-phenylimidazo[1,5-a]quinoline (**3m**).* Synthesized according to the typical procedure and purified by column chromatography (petroleum ether:ethyl acetate = 5:1) to give a light yellow solid (43.8 mg, 68%), mp = 128−130 °C. ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 2.4 Hz, 1H), 7.63−7.59 (m, 2H), 7.55 (s, 1H), 7.53−7.50 (m, 3H), 7.37−7.34 (m, 2H), 7.35−7.23 (m, 1H), 6.92 (d, J = 9.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 142.7, 133.5, 131.3, 130.8, 130.4, 130.1, 129.6, 129.6, 129.0, 127.5, 123.1, 120.3, 119.0, 118.6, 118.4. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{17}H_{17}BrN_2$ 323.0178, found 323.0175. IR (cm^{-1}) ν 2954, 2919, 1470, 1454, 1373, 816, 761.

*9-Methoxy-1-phenylimidazo[1,5-a]quinoline (**3n**).* Synthesized according to typical procedure and purified by column chromatography (petroleum ether:ethyl acetate = 8:1) to give a light yellow solid (41.6 mg, 76%), mp = 115−117 °C. ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 1H), 7.53−7.50 (m, 2H), 7.38−7.34 (m, 2H), 7.32−7.28 (m, 2H), 7.26 (d, J = 4.0 Hz, 1H), 7.21−7.18 (m, 1H), 6.93 (d, J = 9.6 Hz, 1H), 6.78−6.76 (m, 1H), 3.01 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 149.2, 146.8, 136.5, 131.8, 128.6, 128.0, 127.6, 126.0, 125.1, 123.0, 122.5, 120.9, 119.5, 117.8, 109.9, 53.7. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{18}H_{15}N_2O$ 275.1179, found 275.1177. IR (cm^{-1}) ν 2958, 2928, 1469, 1271, 819, 767.

*3-Phenylimidazo[1,5-a]pyridine (**3o**).* Synthesized according to the typical procedure but changing the reaction temperature to room temperature and maintaining for 4 h. Purified by column chromatography (petroleum ether:ethyl acetate = 5:1) to give a light yellow solid (27.9 mg, 72%), mp = 107−109 °C. ^{1}H NMR ($CDCl_3$) δ 8.25−8.23 (m, 1H), 7.80−7.77 (m, 2H), 7.55−7.39 (m, 5H), 6.72−6.70 (m, 1H), 6.55−6.52 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 138.3, 131.7, 130.5, 129.0, 128.7, 128.0, 121.5, 120.7, 118.9, 118.8, 113.1. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{13}H_{11}N_2$ 195.0917, found 195.0915. IR (cm^{-1}) ν 2955, 2921, 1644, 1462, 722.

*3-Isobutylimidazo[1,5-a]pyridine (**3p**).* Synthesized according to the typical procedure but changing the reaction temperature to room temperature and maintaining for 4 h. Purified by column chromatography (petroleum ether:ethyl acetate = 8:1) to give a light yellow oil (21.6 mg, 62%). ^{1}H NMR ($CDCl_3$) δ 7.74−7.72 (m, 1H), 7.41−7.38 (m, 1H), 7.36 (s, 1H), 6.64−6.60 (m, 1H), 6.53−6.49 (m, 1H), 2.85 (d, J = 7.2 Hz, 2H), 2.28−2.21 (m, 1H), 1.0 (d, J = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 138.5, 130.3, 120.7, 118.7, 118.5, 117.6, 112.2, 35.7, 27.7, 22.7. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{11}H_{15}N_2$ 174.1230, found 174.1227. IR (cm^{-1}) ν 2956, 2929, 1465, 1364, 1038, 785, 731.

*6-bromo-3-phenylimidazo[1,5-a]pyridine (**3q**).* Synthesized according to the typical procedure but changing the reaction temperature to room temperature and maintaining for 4 h. Purified by column chromatography (petroleum ether:ethyl acetate = 8:1) to give a light yellow solid (35.7 mg, 66%), mp = 81−83 °C. ^{1}H NMR ($CDCl_3$) δ 8.38−8.36 (m, 1H), 7.77−7.74 (m, 2H), 7.56−7.51 (m, 3H), 7.47−7.43 (m, 1H), 7.39−7.36 (m, 1H), 6.77−6.74 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 138.7, 130.0, 129.8, 129.2, 129.1, 128.0, 122.4, 122.0, 121.3, 119.4, 108.9. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{13}H_{10}BrN_2$ 273.0022, found 273.0018. IR (cm^{-1}) ν 2955, 2922, 1625, 1456, 1328, 909, 763.

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*6-Methyl-3-phenylimidazo[1,5-a]pyridine (**3r**).* Synthesized according to typical procedure but changing the reaction temperature to room temperature and maintaining for 4 h. Purified by column chromatography (petroleum ether:ethyl acetate = 5:1) to give a light yellow solid (30.4 mg, 73%), mp = 71−73 °C. ^{1}H NMR ($CDCl_3$) δ 8.03−8.01 (m, 1H), 7.79−7.76 (m, 2H), 7.53−7.48 (m, 3H), 7.43−7.37 (m, 2H), 6.58−6.56 (m, 1H), 2.21 (d, J = 1.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 137.8, 130.9, 130.7, 129.0, 128.5, 128.0, 122.6, 122.4, 120.5, 118.5, 118.1, 18.6. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}N_2$ 209.1073, found 209.1069. IR (cm^{-1}) ν 2923, 2853, 1602, 1454, 805, 768.

*1-Phenylimidazo[1,5-a]quinoxaline (**3s**).* Synthesized according to typical procedure and purified by column chromatography (petroleum ether:ethyl acetate = 5:1) to give a light yellow solid (41.6 mg, 85%), mp = 114−116 °C. ^{1}H NMR ($CDCl_3$) δ 8.91 (s, 1H), 7.96−7.94 (m, 1H), 7.90 (s, 1H), 7.69−7.65 (m, 2H), 7.59−7.53 (m, 3H), 7.51−7.49 (m, 2H), 7.45−7.43 (m, 1H), 7.24−7.19 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 145.5, 143.7, 137.2, 132.3, 130.3, 130.1, 129.7, 129.0, 127.7, 127.0, 126.8, 126.7, 126.0, 116.6. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}N_3$ 246.1026, found 246.1024. IR (cm^{-1}) ν 2955, 2918, 1454, 1385, 1261, 796.

*3-Phenylimidazo[5,1-a]isoquinoline (**3t**).* Synthesized according to typical procedure and purified by column chromatography (petroleum ether:ethyl acetate = 5:1) to give a light yellow solid (43.9 mg, 90%), mp = 137−139 °C. ^{1}H NMR ($CDCl_3$) δ 8.01−7.99 (m, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.77−7.74 (m, 2H), 7.52−7.41 (m, 5H), 7.39−7.37 (m, 1H), 7.72 (d, J = 7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 141.0, 130.2, 129.4, 129.0, 128.9, 128.45, 128.42, 126.99, 126.97, 125.1, 122.4, 120.8, 120.6, 113.9. HRMS(APCI-FTMS) m/z: $[M + H]^+$ calcd for $C_{17}H_{13}N_2$ 245.1073, found 245.1071. IR (cm^{-1}) ν 2954, 2921, 1449, 1369, 793, 702.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra for all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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