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Facile, efficient synthesis of polyfunctionalized 2-aminoimidazoles via vinyl azides and cyanamide

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ABSTRACT

A simple and direct synthesis of 2-aminoimidazoles from vinyl azides and cyanamide was developed. An attractive feature of this protocol is that the desired products are generated in a highly efficient and eco-friendly manner without the use of a catalyst. A plausible mechanism has been proposed.

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1. Introduction

2-Aminoimidazoles are one of the most important heterocyclic motifs in organic chemistry, they are the central feature of alkaloids and many biologically active substances.[1] As a result, the development of methods for the preparation of these molecules has attracted considerable attention. A number of methods have been developed for the synthesis of 2-aminoimidazoles, such as a cyclocondensation between diketones with guanidine followed by catalytic hydrogenation;[2] the reaction of α-halo ketones with *N*-acetylguanidine;[3] the iminophosphorane-mediated cyclization of α-azido esters;[4] the synthesis of 2-aminoimidazoles by the formation of imidazo[1,2-α]pyrimidines followed by cleavage of the pyrimidine ring with hydrazine or amines;[5] and the ammonolysis of 2-amino-1,3-oxazol-3-ium salts.[6] Some of the common synthetic approaches either need a prolonged reaction time, difficult experimental procedures, expensive transition metal additives, complex substrates, or in unsatisfied yields.[2–6] Furthermore, polyfunc tionalized 4,5-disubstututed-2-aminoimidazoles are not readily available through general methods.

Therefore, the development of improved methods for the synthesis of 2-aminoimidazoles is of importance.

Herein, we report a novel, facile approach to provide polyfunctionalized 2-aminoimidazoles using vinyl azides and cyanamide. An attractive feature of this protocol is that the desired product could be generated in a highly efficient and eco-friendly manner.

2. Results and discussion

Initially, (*Z*)-2-azido-1,3-diphenylprop-2-en-1-one and cyanamide were selected as reagents in order to optimize the reaction condition. Firstly, a range of solvents were screened (Table 1, entries 1–6). It was determined that ethanol (Table 1, entry 3) was superior to other aprotic and protic solvents. In order to further improve the reaction conditions, a range of bases were tested as additives (Table 1, entries 7–13). When an inorganic base, such as Cs_2CO_3, K_2CO_3 or NaOAc was added into the reaction, no significant improvement in product yields was identified. Moreover, NaOH was found to be destructive to this reaction (Table 1, entry 10). Conversely the yield of the desired product was significantly improved when an organic base like Et_3N or DBU was used in this reaction (Table 1, entries 12 and 13). However, when DMAP was used, the yield declined significantly (Table 1, entry 11). The reaction was also assessed at a lower temperature but this resulted in a decrease in the yield (Table 1, entries 14 and 15). On the basis of this initial study, the most efficient reaction condition occurred when (*Z*)-2-azido-1,3-diphenylprop-2-en-1-one (1 equiv), cyanamide (2 equiv), and

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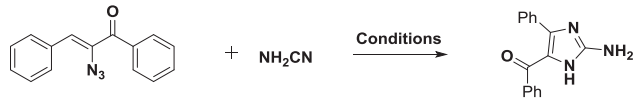
Table 1
Optimization of reaction conditions[a]



Entry	Additive	Solvent	T (°C)	Conversion (%)
1	—	CH_3CN	90	53%
2	—	THF	90	34%
3	—	DMF	90	Trace
4	—	1,4-Dioxane	90	21%
5	—	Toluene	90	52%
6	—	Ethanol	90	64%
7	Cs_2CO_3	Ethanol	90	66%
8	K_2CO_3	Ethanol	90	67%
9	NaOAc	Ethanol	90	72%
10	DMAP	Ethanol	90	30%
11	NaOH	Ethanol	90	Trace
12	DBU	Ethanol	90	85%
13	**Et_3N**	**Ethanol**	90	**90%**
14	Et_3N	Ethanol	40	23%
15	Et_3N	Ethanol	60	50%

[a] Reaction conditions: (*Z*)-2-azido-1,3-diphenylprop-2-en-1-one(0.5 mmol, 1.0 equiv), cyanamide (1 mmol, 2 equiv), base (0.5 mmol, 1 equiv), 2 mL of solvent, 6 h, 90 °C. The most efficient entry is highlighted in bold.

Et_3N(1 equiv) were mixed in ethanol at 90 °C for 6 h (Table 1, entry 14).

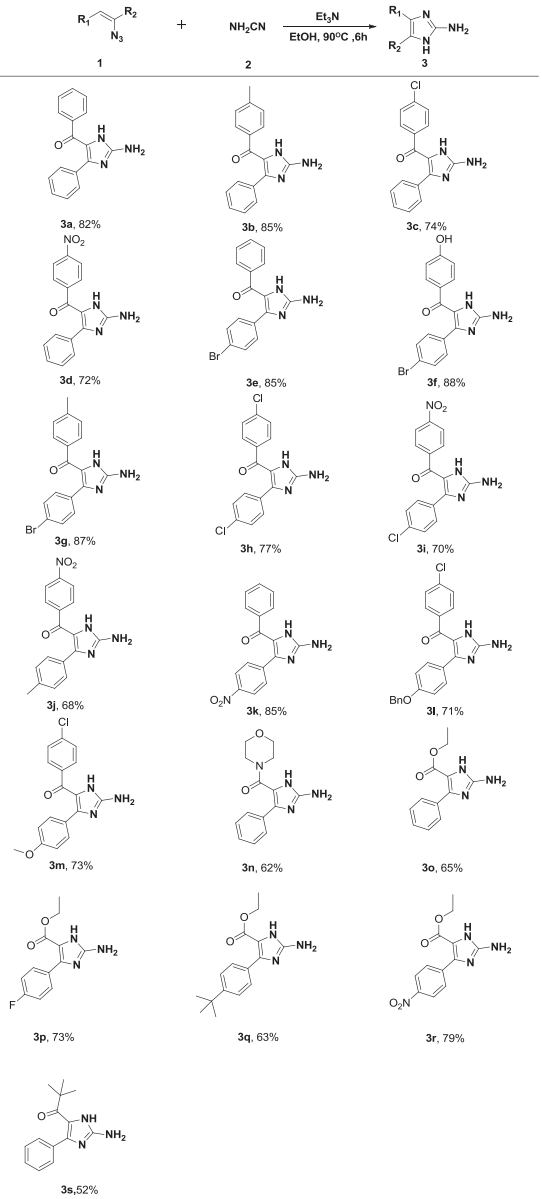
With the optimized reaction condition in hand, the scope of the reaction was studied using a set of vinyl azides **1** and cyanamide (Table 2). The α-azidovinylketones were readily prepared from the corresponding olefins by successive reaction with bromine then with sodium azide. And the α-azidovinylesters were prepared from the corresponding aldehydes with ethyl azidoacetate.[7] The result reveals that various substituted vinyl azides bearing several functional groups worked well with cyanamide to provide the desired products. In general, α-azidovinylketones worked more efficiently in these conditions when compared to the α-azidovinylesters (Table 2). α-Azidovinylketones with electron-deficient groups at the R_1 position performed slightly better (**3e** and **3k** compared to **3a**; **3g** compared to **3b**; **3h** compared to **3m**, **3l** and **3c**). While at the R_2 position, relatively strong electron-donating groups gave slight increases in yields (**3g** and **3f** compared to **3e**; **3b** compared to **3a**). Not surprisingly, when a morpholinylcarbonyl group was present at the R_2 position (Table 2, **3n**) the final yield was lower compared to **3a** and **3o**.

The structures of the polyfunctionalized 2-aminoimidazoles **3** were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. Furthermore, the structure of **3k** was confirmed by X-ray crystal structure analysis as shown in Fig. 1. On the basis of the results above, we proposed the following possible mechanism for this reaction, as shown in Scheme 1. The likely first step is a Michael addition–elimination of the cyanamide **2** to the vinyl azides **1** affording an active intermediate **I**, driven by the excellent leaving-group ability of nitrogen. Subsequently, the reaction undergoes an intramolecular condensation to give the desired product **3**.

3. Conclusions

In conclusion, we have developed a facile approach to provide functionalized 2-aminoimidazoles, which are ubiquitous structural units in a number of biologically active compounds. The synthesis is economical both in lost atom count and reaction materials. This novel reaction provides products in good yields via a domino process involving sequential cyclization and intramolecular rearrangement. This simple synthesis with the ability to incorporate multiple functional groups into a desired imidazole ring system provides an attractive strategy for pharmaceutical building blocks and medicinal chemistry applications.

Table 2
Scope of the reaction of vinyl azides and cyanamide under optimal conditions[a]



[a]Reaction conditions: vinyl azides (0.4mmol, 1.0equiv), cyanamide(0.8mmol, 2equiv), Et_3N(0.4mmol,1 equiv) 2mL of solvent, 6h, 90 °C.Isolated yield.

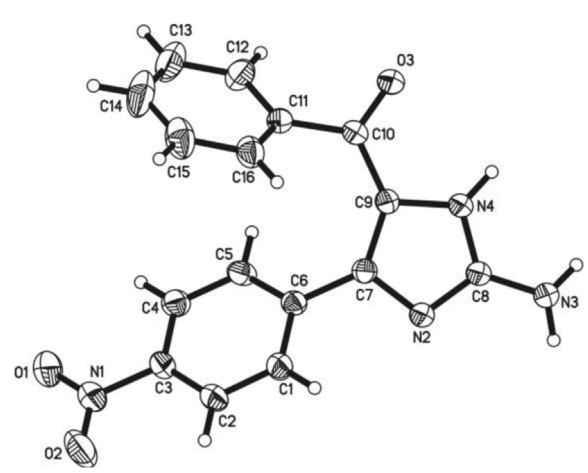
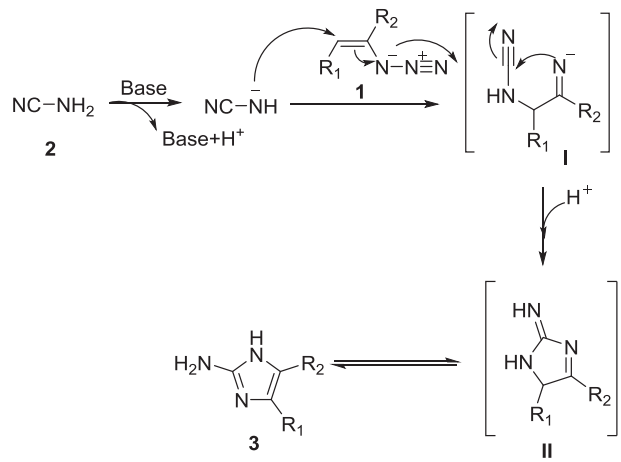


Fig. 1. X-ray crystal structure of **3k**.



Scheme 1. Proposed mechanism for the synthesis of 4,5-disubstituted-2-amino-imidazoles.

4. Experimental section

4.1. General

All solvents were purified according to standard methods prior to use. Melting points were recorded on a BÜCHI B-540 melting point apparatus. NMR spectra were recorded for ^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz. For ^{1}H NMR, tetramethyl-silane (TMS) served as internal standard (δ=0) and data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), and coupling constant (s) in Hertz. For ^{13}C NMR, TMS (δ=0) or DMSO (δ=40.45) was used as internal standard and spectra were obtained with complete proton decoupling. LC/MS and HRMS data was obtained using Agilent Technologies 6224 TOF LC/MS. The starting material vinyl azides **1a-1s** were prepared according to literature methods.[7] The starting material **2** (cyanamide, 50% aqueous solution) was commercially available.

4.2. General procedure for the synthesis of 2-aminoimidazoles

A mixture of α-azidovinylester or α-azidovinylketone **1** (0.4 mmol), cyanamide **2** (0.8 mmol), Et_3N (0.4 mmol) was stirred in absolute ethanol 2 mL at 90 °C for 6 h. After the completeness of the reaction, the reaction was diluted with water and extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated, and purified by flash chromatography (DCM/MeOH) on silica gel to afford **3a-3s**.

*4.2.1. 4-Phenyl-5-benzoyl-1H-imidazol-2-amine (**3a**).* Yield: 82%, white solid, mp: 245.1–247.3 °C; ^{1}H NMR (500 MHz, DMSO): δ 10.98 (s, 1H), 7.40 (d, J=6.9 Hz, 2H), 7.36–7.31 (m, 1H), 7.26 (d, J=6.7 Hz, 2H), 7.21–7.15 (m, 2H), 7.12 (d, J=6.6 Hz, 1H), 7.07 (d, J=6.8 Hz, 2H), 6.02 (s, 2H); ^{13}C NMR (125 MHz, DMSO): δ 183.5, 153.4, 149.3, 139.5, 135.1, 131.2, 129.6, 129.0, 128.1, 127.8, 127.7, 122.4; HRMS–EI calcd for $C_{16}H_{13}N_3O$: 263.1059; Found: 263.1054.

*4.2.2. 4-Phenyl-5-(4-methylbenzoyl)-1H-imidazol-2-amine (**3b**).* Yield: 85%, light yellow solid, mp: 249.1–249.5 °C; ^{1}H NMR (500 MHz, DMSO): δ 10.94 (s, 1H), 7.31 (m, 4H), 7.09–7.14 (m, 3H), 7.00 (m, 2H), 5.98 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, DMSO): δ 183.3, 153.1, 148.6, 141.3, 136.8, 135.1, 129.5, 129.3, 128.7, 127.8, 127.7, 122.3, 21.4; HRMS–EI calcd for $C_{17}H_{15}N_3O$: 277.1215; Found: 277.1213.

*4.2.3. 4-Phenyl-5-(4-chlorobenzoyl)-1H-imidazol-2-amine (**3c**).* Yield: 74%, light yellow solid, mp: 253.5–254.4 °C; ^{1}H NMR (500 MHz, DMSO): δ 11.07 (s, 1H), 7.37 (m, 2H), 7.22 (m, 5H), 7.11 (m, 2H), 6.08 (s, 2H); ^{13}C NMR (125 MHz, DMSO): δ 182.2, 153.4, 149.9, 138.3, 135.9, 134.7, 131.0, 129.6, 128.1, 128.0, 127.8, 122.3; HRMS–EI calcd for $C_{16}H_{12}ClN_3O$: 297.0669; Found: 297.0661.

*4.2.4. 4-Phenyl-5-(4-nitrobenzoyl)-1H-imidazol-2-amine (**3d**).* Yield: 72%, yellow solid, mp: 205.2–206.9 °C; ^{1}H NMR (500 MHz, DMSO): δ 11.19 (s, 1H), 7.94 (m, 2H), 7.55 (m, 2H), 7.12–7.17 (m, 3H), 7.04 (m, 2H), 6.22 (s, 2H); ^{13}C NMR (125 MHz, DMSO): δ 181.0, 154.1, 151.6, 148.5, 145.6, 134.6, 130.3, 129.7, 128.2, 127.8, 123.3, 122.6; HRMS–EI calcd for $C_{16}H_{12}N_4O_3$: 308.0909; Found: 308.0908.

*4.2.5. 4-(4-Bromophenyl)-5-benzoyl-1H-imidazol-2-amine (**3e**).* Yield: 85%, light yellow solid, mp: 275.2–276.5 °C; ^{1}H NMR (500 MHz, DMSO): δ 11.07 (s, 1H), 7.46 (m, 2H), 7.41 (t, J=7.8 Hz, 1H), 7.36–7.22 (m, 6H), 6.02 (s, 2H). ^{13}C NMR (125 MHz, DMSO): δ 184.0, 153.0, 139.5, 133.8, 131.4, 130.7, 129.2, 128.5, 128.3, 127.9, 121.1; HRMS–EI calcd for $C_{16}H_{12}BrN_3O$: 341.0164; Found: 341.0161.

*4.2.6. 4-(4-Bromophenyl)-5-(4-hydroxybenzoyl)-1H-imidazol-2-amine (**3f**).* Yield: 88%, white solid, mp: 255.1–255.3 °C; ^{1}H NMR (500 MHz, DMSO): δ 10.97 (s, 1H), 10.03 (s, 1H), 7.35 (m, 6H), 6.64 (m, 2H), 5.89 (s, 2H). ^{13}C NMR (125 MHz, DMSO): δ 180.5, 161.1, 152.6, 131.9, 131.9, 131.7, 131.7, 131.3, 130.8, 130.2, 120.8, 115.0; HRMS–EI calcd for $C_{16}H_{12}BrN_3O_2$: 357.0113; Found: 357.0111.

*4.2.7. 4-(4-Bromophenyl)-5-(4-methylbenzoyl)-1H-imi-dazol-2-amine (**3g**).* Yield: 87%, light yellow solid, mp: 259.8–261.5 °C; ^{1}H NMR (500 MHz, DMSO): δ 11.02 (s, 1H), 7.31 (m, 6H), 7.08 (m, 2H), 6.02 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 183.3, 153.1, 147.2, 141.5, 136.8, 134.4, 131.4, 130.7, 129.2, 128.9, 122.4, 121.0, 21.4; HRMS–EI calcd for $C_{17}H_{14}BrN_3O$: 355.0320; Found: 355.0326.

*4.2.8. 4-(4-Chlorophenyl)-5-(4-chlorobenzoyl)-1H-imidazol-2-amine (**3h**).* Yield: 77%, yellow solid, mp: 263.2–265.4 °C; ^{1}H NMR (500 MHz, DMSO): δ 11.79 (s, 1H), 7.50 (d, J=7.5 Hz, 2H), 7.36 (d, J=8.2 Hz, 2H), 7.32 (d, J=8.3 Hz, 2H), 7.24 (d, J=8.3 Hz, 2H), 6.38 (s, 2H). ^{13}C NMR (125 MHz, DMSO): δ 152.3, 137.8, 136.4, 133.1, 131.6, 131.3, 131.1, 129.2, 128.4, 128.3, 128.0; HRMS–EI calcd for $C_{16}H_{11}Cl_2N_3O$: 331.0279; Found: 331.0275.

*4.2.9. 4-(4-Chlorophenyl)-5-(4-nitrobenzoyl)-1H-imidazol-2-amine (**3i**).* Yield: 70%, yellow solid, mp: 283.4–285.6 °C; ^{1}H NMR (500 MHz, DMSO): δ 11.24 (s, 1H), 8.06 (d, J=7.9 Hz, 2H), 7.76–7.58 (m, 2H), 7.34 (m, 2H), 7.20 (m, 2H), 6.57 (m, 2H), 6.17 (s, 2H); ^{13}C NMR (125 MHz, DMSO): δ 184.3, 163.3, 148.6, 145.5, 133.0, 131.3, 130.4, 127.9, 123.7, 123.3, 118.8, 106.4; HRMS–EI calcd for $C_{16}H_{11}ClN_4O_3$: 342.0520; Found: 342.0517.

*4.2.10. 4-(4-Methylphenyl)-5-(4-nitrobenzoyl)-1H-imidazol-2-amine (**3j**).* Yield: 68%, light yellow solid, mp: 296.3–297.1 °C. ^{1}H NMR (500 MHz, DMSO): δ 11.24 (s, 1H), 8.00 (m, 2H), 7.63 (m, 2H), 7.17 (m, 2H), 6.92 (m, 2H), 6.15 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, DMSO): δ 180.8, 154.1, 151.8, 148.4, 145.8, 137.7, 130.26, 130.2, 129.6, 128.5, 128.4, 123.1, 122.5, 21.1; HRMS–EI calcd for $C_{17}H_{14}N_4O_3$: 322.1066; Found: 322.1069.

*4.2.11. 4-(4-Nitrophenyl)-5-benzoyl-1H-imidazol-2-amine (**3k**).* Yield: 85%, light yellow solid, mp: 271.4–272.3 °C; ^{1}H NMR (500 MHz, DMSO): δ 11.25 (s, 1H), 7.96 (d, J=8.8 Hz, 2H), 7.96 (d, J=8.8 Hz, 2H), 7.62 (d, J=8.8 Hz, 2H), 7.47 (d, J=7.2 Hz, 2H), 7.42 (t, J=7.5 Hz, 1H), 7.26 (t, J=7.6 Hz, 2H), 6.12 (s, 2H); ^{13}C NMR (125 MHz, DMSO): δ 183.7, 153.5, 146.5, 146.1, 141.7, 139.3, 131.7, 130.4, 129.1,

128.4, 123.5, 122.9; HRMS–EI calcd for $C_{16}H_{12}N_4O_3$: 308.0909; Found: 308.0907.

*4.2.12. 4-(4-(Benzyloxy)phenyl)-5-(4-chlorobenz-oyl)-1H-imidazol-2-amine (**3l**).* Yield: 71%, light yellow solid, mp: 243.1–245.2 °C; ^{1}H NMR (500 MHz, DMSO): δ 10.93 (s, 1H), 7.42–7.33 (m, 7H), 7.29–7.19 (m, 4H), 6.75 (d, J=8.3 Hz, 2H), 6.05 (s, 2H), 5.05 (s, 2H); ^{13}C NMR (125 MHz, DMSO): δ 181.7, 158.4, 153.5, 149.9, 138.5, 137.4, 135.7, 131.0, 130.8, 128.8, 128.3, 128.2, 127.9, 127.6, 121.9, 114.2, 69.6; HRMS–EI calcd for $C_{23}H_{18}ClN_3O_2$: 403.1088; Found: 403.1085.

*4.2.13. 4-(4-Methoxyphenyl)-5-(4-chlorobenzoyl)-1H-imidazol-2-amine (**3m**).* Yield: 73%, light yellow solid, mp: 278.1–280.3 °C; ^{1}H NMR (500 MHz, DMSO): δ 11.00 (s, 1H), 7.47 (m, 2H), 7.28 (m, 4H), 6.71 (d, J=7.9 Hz, 2H), 6.02 (s, 2H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, DMSO): δ 172.5, 163.2, 159.3, 152.8, 138.5, 135.8, 131.0, 130.9, 128.2, 118.7, 113.4, 112.9, 55.5; HRMS–EI calcd for $C_{17}H_{14}ClN_3O_2$: 327.0775; Found: 327.0778.

*4.2.14. 4-Phenyl-5-(morpholine-4-carbonyl)-1H-imidazol-2-amine (**3n**).* Yield: 62%, white solid, mp: 176.6–177.8 °C; ^{1}H NMR (500 MHz, DMSO): δ 11.02 (s, 1H), 7.48 (d, J=7.5 Hz, 2H), 7.34 (t, J=7.8 Hz, 2H), 7.21 (t, J=7.3 Hz, 1H), 5.45 (s, 2H), 3.44 (m, 8H); ^{13}C NMR (125 MHz, DMSO): δ 164.6, 163.3, 150.5, 132.6, 128.7, 126.8, 126.4, 118.8, 66.5, 45.0; HRMS–EI calcd for $C_{14}H_{16}N_4O_2$: 272.1273; Found: 272.1278.

*4.2.15. Ethyl 2-amino-4-phenyl-1H-imidazole-5-carboxylate (**3o**).* Yield: 65%, light yellow solid, mp: 148.6–150.1 °C; ^{1}H NMR (500 MHz, DMSO): δ 10.89 (s, 1H), 7.90 (d, J=7.4 Hz, 2H), 7.35 (t, J=7.4 Hz, 2H), 7.30 (m, 1H), 5.44 (s, 2H), 4.17 (q, J=7.1 Hz, 2H), 1.24 (t, J=7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO): δ 172.5, 160.0, 151.6, 133.7, 130.4, 129.2, 128.2, 127.9, 59.8, 14.7. HRMS–EI calcd for $C_{12}H_{13}N_3O_2$: 231.1008; Found: 231.1009.

*4.2.16. Ethyl 2-amino-4-(4-fluorophenyl)-1H-imidazole-5-carboxylate (**3p**).* Yield: 73%, white solid, mp: 176.2–179.8 °C; ^{1}H NMR (500 MHz, DMSO): δ 10.96 (s, 1H),7.97 (dd, J=8.9, 5.8 Hz, 2H), 7.18 (t, J=9.0 Hz, 2H), 5.86 (s, 2H), 4.17 (q, J=7.1 Hz, 2H), 1.24 (t, J=7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO): δ 184.3, 163.1, 161.1, 160.0, 151.9, 131.2, 131.1, 130.6, 114.8, 114.6, 59.8, 14.7; HRMS–EI calcd for $C_{12}H_{12}FN_3O_2$: 249.0914; Found: 249.0910.

*4.2.17. Ethyl 2-amino-4-(4-tert-butylphenyl)-1H-imidazole-5-carboxylate (**3q**).* Yield: 63%, white solid, mp: 209.8–210.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, J=8.4 Hz, 2H), 7.37 (d, J=8.5 Hz, 2H), 4.20 (q, J=7.1 Hz, 2H), 1.31 (s, 9H), 1.22 (t, J=7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO): δ 160.1, 151.9, 151.8, 150.5, 131.4, 128.9, 124.6, 112.5, 59.6, 34.7, 31.5, 14.8; HRMS–EI calcd for $C_{16}H_{21}N_3O_2$: 287.1634; Found: 287.1635.

*4.2.18. Ethyl 2-amino-4-(4-nitrophenyl)-1H-imidazole-5-carboxylate (**3r**).* Yield: 79%, white solid, mp: 264.1–265.5 °C; ^{1}H NMR (500 MHz, DMSO): δ 11.14 (s, 1H), 8.24 (q, J=9.1 Hz, 4H), 5.89 (s, 2H), 4.22 (q, J=7.1 Hz, 2H), 1.27 (t, J=7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO): δ 159.6, 152.4, 146.7, 143.4, 141.1, 129.9, 123.3, 113.9, 60.3, 14.7; HRMS–EI calcd for $C_{12}H_{12}N_4O_4$: 276.0859; Found: 276.0858.

*4.2.19. 4-Phenyl-5-pivaloyl-1H-imidazol-2-amine (**3s**).* Yield: 52%, white solid, mp: 196.5–197.9 °C; ^{1}H NMR (500 MHz, DMSO): δ 11.20 (s, 1H), 7.57 (d, J=7.0 Hz, 2H), 7.35 (t, J=6.5 Hz, 2H), 7.29 (m, 1H), 5.54 (s, 2H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, DMSO): δ 204.3, 154.0, 136.9, 133.8, 132.8, 132.6, 48.5, 32.3.HRMS–EI calcd for $C_{14}H_{17}N_3O$: 243.1372; Found: 243.1370.

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Supplementary data

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all products. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.01.007.

References and notes

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