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Copper-catalyzed three-component reaction to synthesize polysubstituted imidazo[1,2-*a*]pyridines†

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An efficient three-component one-pot and operationally simple cascade of 2-aminopyridines with sulfonyl azides and terminal ynones is reported, providing a variety of polysubstituted imidazo[1,2-*a*]pyridine derivatives in moderate to excellent yields. In particular, the reaction goes through a CuAAC/ring-cleavage process and forms a highly active intermediate α -acyl-*N*-sulfonyl ketenimine with base free.

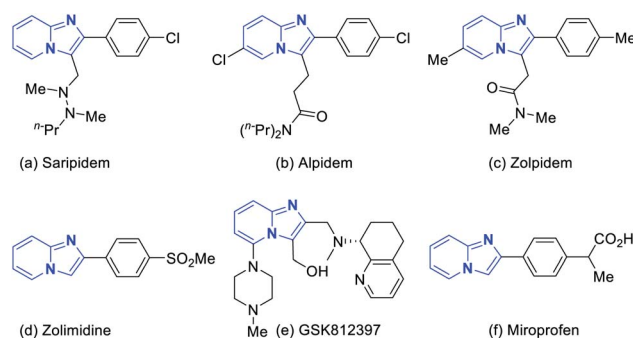
Polysubstituted imidazo[1,2-*a*]pyridines are well established as privileged scaffolds which are commonly encountered in many bioactive natural products and biological molecules that may be good drug candidates.¹ Most imidazo[1,2-*a*]pyridines possess various biological activities, like antibacterial,² anti-inflammatory,³ antiviral,⁴ and anticancer.⁵ Some of the imidazo[1,2-*a*]pyridine derivatives are commercially available drugs, including Saripidem,⁶ Alpidem,⁷ Zolpidem,⁸ Zolimidine,⁹ Miroprofen¹⁰ and drug candidates GSK812397 (Fig. 1).¹¹ Therefore, the development of novel methods for the synthesis of these imidazo[1,2-*a*]pyridines is important in the field of synthetic organic and pharmaceutical chemistry.

In the past few years, reactions utilizing Cu,¹² Pd,¹³ Mn,¹⁴ TEMPO-mediated,¹⁵ I₂ (ref. 16) and a few other catalysts¹⁷ have provided attractive and valuable routes for the construction of imidazo[1,2-*a*]pyridines. However, most reactions can only produce monosubstituted imidazo[1,2-*a*]pyridines or halogenated intermediates (Scheme 1a)¹⁸ which can undergo one more steps of coupling reaction leading to polysubstituted products. Therefore, developing one-pot synthetic reactions will provide a direct and powerful tool to meet these challenges. To the best of our knowledge, imidazo[1,2-*a*]pyridines can be synthesized from 2-aminopyridines, terminal alkyne and aldehyde in a three-component coupling reaction, catalyzed by copper, in one pot (Scheme 1b).¹⁹ However, aldehydes are unstable and easily oxidized. They are environmentally unfriendly for

synthesis or complex procedures. Under this background, the development of multicomponent one-pot synthetic strategies for the preparation of polysubstituted imidazo[1,2-*a*]pyridines still remains highly desirable.

Previous studies reported that the copper-catalyzed multicomponent reactions (MCRs) of sulfonyl azides, terminal alkynes and other components (CuAAC/ring-cleavage reaction) has been applied to synthesize numerous oxygen- and nitrogen-containing heterocyclic compounds.²⁰ However, the reaction generally carried out under strong base conditions, and limited the application of some substrates, such as terminal ynones, which will take a self-condensation under the base conditions.²¹ Thus, the neutral or weak acidic conditions have developed by our group and the terminal ynones successfully used in CuAAC/ring-cleavage reaction to form a highly active intermediate α -acyl-*N*-sulfonyl ketenimines.²² Accordingly, an efficient one-pot and operationally three-component reaction of 2-aminopyridines, sulfonyl azides and terminal ynones is reported (Scheme 1c).

Our initial study began with an examination of the synthesis of imidazo[1,2-*a*]pyridine **4a** from 2-aminopyridine (**1a**), ethyl


 Fig. 1 Some imidazo[1,2-*a*]pyridine drugs or drug candidates.

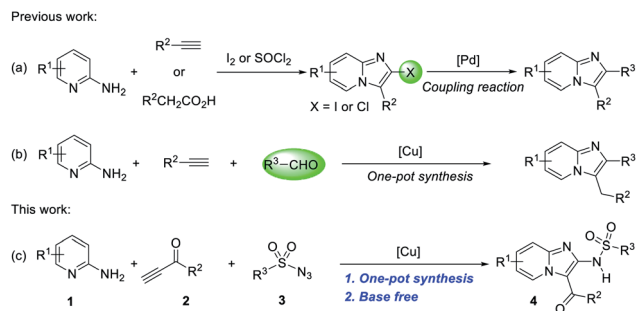
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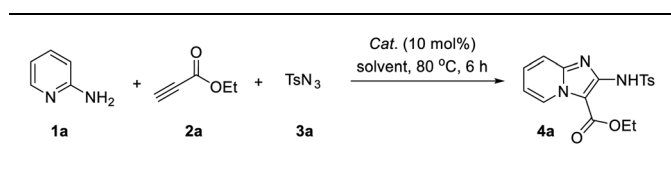
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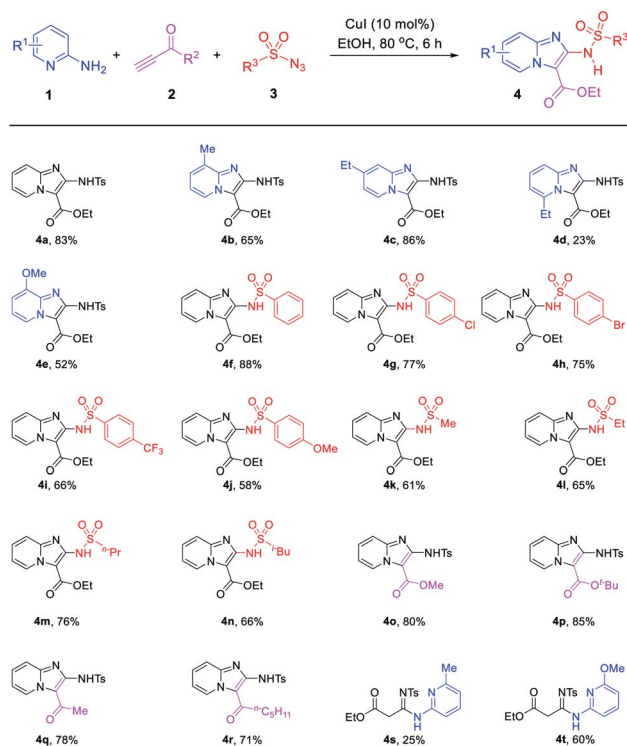
Scheme 1 Synthesis of polysubstituted imidazo[1,2-*a*]pyridines.

propiolate (**2a**) and *p*-tosyl azide (**3a**). Initial screenings involved using CuI as catalyst and no additive with a variety of solvents in a range of standard solvents. These results revealed that the desired conversion could be effected in most solvents (Table 1, entries 1–9), with EtOH delivering product **4a** in highest yield (83%). The other solvents give a comparable yields, such as DCE, toluene, MeCN and THF, while the DMSO and DMF gave the **4a** lowest yield of 26% and 35%. Thus, the optimal solvent was determined to be EtOH. Encouraged by this promising result, variety of catalysts were screened. Among the copper catalysts used, most Cu-catalysts exhibited the high catalytic reactivity in this reaction whether it's Cu^I-catalysts or Cu^{II}-catalysts (Table 1, entries 10–13). However, Cu(OTf)₂ exhibited low efficiencies for this reaction, and other catalysts, such as AgOAc failed to produce the desired product (Table 1, entries 14

Table 1 Optimization of catalytic conditions^a

Entry	Cat.	Solvent	Yield ^b (%) 4a
1	CuI	CHCl ₃	74
2	CuI	DCE	77
3	CuI	Toluene	78
4	CuI	MeCN	80
5	CuI	THF	62
6	CuI	1,4-Dioxane	44
7	CuI	DMSO	26
8	CuI	DMF	35
9	CuI	EtOH	83
10	CuCl	EtOH	75
11	CuBr	EtOH	73
12	CuBr ₂	EtOH	70
13	Cu(OAc) ₂	EtOH	50
14	Cu(OTf) ₂	EtOH	32
15	AgOAc	EtOH	nd ^c
16	CuI	EtOH	80 ^d
17	CuI	EtOH	76 ^e

^a Reaction conditions: **1a** (1.0 mmol), cat. (10 mol%) in the solvent (3 mL) was added **2a** (1.5 mmol) and **3a** (1.5 mmol) stirring at 80 °C for 6 h. ^b Isolated yields. ^c nd = not detected the target product. ^d The reaction temperature was 70 °C. ^e The temperature was 90 °C.

Table 2 Substrate scopes^a

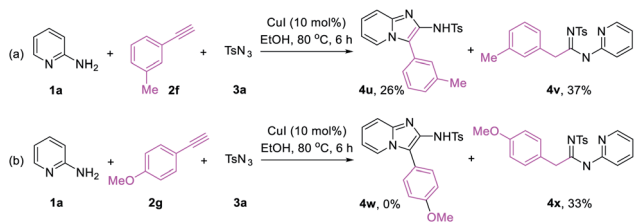
^a Unless otherwise noted, the reaction conditions were as follow: **1** (1.0 mmol), CuI (10 mol%) in the MeCN (3 mL) was added **2** (1.5 mmol), **3** (1.5 mmol) stirring at 80 °C for 6 h.

and 15). Lastly, the effect of temperature was evaluated. Screening results revealed that the reaction temperature above or below 80 °C decreased the reaction yield (Table 1, entries 16 and 17).

Under the optimized conditions (Table 1, entries 9), the capacity of this reaction to affect the coupling of a range of different substrates was investigated. Agreeably, as shown in Table 2, various 2-aminopyridines, with an alkyl group or methoxy group, all exhibited good functional group tolerance to obtain the desired products (**4a–4c**, **4e**). However, the 2-aminopyridines with electron-withdrawing nature can't obtain the desired products. In addition, due to steric hindrance, some 2-aminopyridines obtained the products with low yield or cannot be separated to obtain the desired products. Such as 6-ethyl-2-aminopyridine (**1d**) obtained the product **4d** with low yield and 6-methyl-2-aminopyridine (**1f**) or 6-methoxy-2-aminopyridine (**1g**) obtained the uncyclized products **4s** and **4t**.

Next, the scope and limitation of the terminal ynone **2** and sulfonyl azide **3** substrates were tested. It is noteworthy that the sulfonyl azide substrates showed slight influences on this reaction. With R³ changed by aromatic or aliphatic substituents, such as -Ph, -(4-ClC₆H₄), -(4-CF₃C₆H₄), -(4-OMeC₆H₄), -Me and -*n*-Bu, the reaction could smoothly give the anticipated products (**4f–4n**) in comparable yields. The substrates R² bearing the -OMe, -O^tBu, -Me and other alkyl group also can obtain **4o–4r** in good yields.





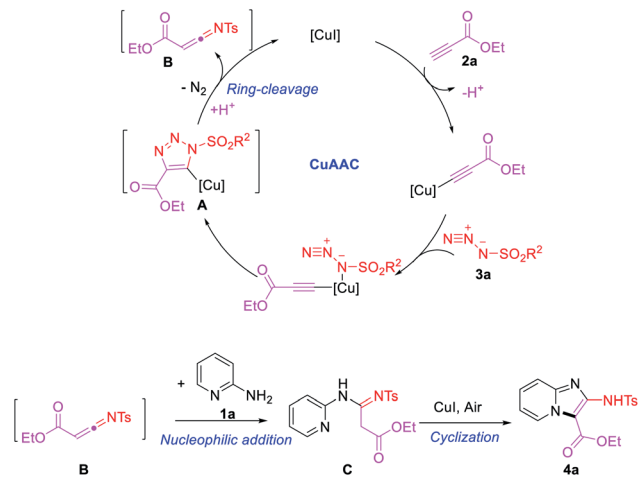
Scheme 2 Investigation the reaction of 2-aminopyridine (1a), aryl acetylenes (2f, 2g) and *p*-tosyl azide (3a).

In order to broaden the suitability of substrates, we also investigated other terminal alkynes, such as aryl acetylenes. The experiments revealed that some aryl acetylene such as 3-methyl phenylacetylene can obtain imidazo[1,2-*a*]pyridine **4u** with low yield of 26% and an uncyclized linear product **4v** (Scheme 2a). Most aryl acetylenes such as 4-methoxy phenylacetylene only obtain uncyclized products (Scheme 2b). It shows that the reactivity of terminal ynones is higher than that of traditional terminal alkyne.

None of the product imidazo[1,2-*a*]pyridines **4a–4r** have been reported previously, which were subject to full spectroscopic characterization (see ESI† for details) and the derived data were in complete accord with the assigned structures. And **4a** was confirmed by single-crystal X-ray analysis (Fig. 2).

A possible reaction pathway for the formation of imidazo[1,2-*a*]pyridine (**4a**) from precursors **1a**, **2a** and **3a** is shown in Scheme 3. Thus, in keeping with earlier proposals,^{19,21} the substrates **2a** and **3a** are expected to react, in the presence of the copper(i) catalyst to form the metallated triazole **A** through the CuAAC procedure. Then, the complex **A** undergo a ring-cleavage rearrangement leading to a highly active intermediate *N*-sulfonyl- α -acylketenimine **B**. This last species **B** is captured by **1a** via nucleophilic addition to generate the intermediate **C**, which deliver the observed product **4a** by intramolecular oxidative coupling similar to literature.²³ Otherwise, due to the poor activity, most of the traditional terminal alkynes involved in the reaction will stop in the intermediate **C** leading the uncyclized products.

In summary, we have developed an original approach for the synthesis of polysubstituted imidazo[1,2-*a*]pyridines from a mixture of the corresponding 2-aminopyridines, sulfonyl azides and terminal ynones, through CuAAC/ring-cleavage



Scheme 3 Plausible reaction mechanism.

process and generated a highly active intermediate α -acyl-*N*-sulfonyl ketenimines. More detailed novel reactions and the investigation of new applications of this intermediate are now being undertaken in our laboratory.

Experimental

General

All melting points were determined on a Yanaco melting point apparatus and were uncorrected. IR spectra were recorded as KBr pellets on a Nicolet FT-IR 5DX spectrometer. All spectra of ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) were recorded on a JEOL JNM-ECA 400 spectrometer in DMSO-*d*₆ or CDCl₃ (otherwise as indicated) with TMS was used as an internal reference and *J* values are given in Hz. HRMS were obtained on a Thermo Scientific Q Exactive Focus Orbitrap LC-MS/MS spectrometer.

Preparation and characterizations of compounds 4a–4x

Ethyl-2-((4-methylphenyl)sulfonamido)imidazo[1,2-*a*]pyridine-3-carboxylate (**4a**). To a solution of CuI (19.5 mg, 0.10 mmol) in EtOH (3 mL) was added pyridin-2-amine (**1a**, 94.2 mg, 1 mmol), ethyl propiolate (**2a**, 147 mg, 1.5 mmol), TsN₃ (295.8 mg, 1.5 mmol). After the mixture was stirred at 80 °C for 6 h (monitored by TLC), the solvent was removed. The residue was purified *via* flash chromatography (silica gel, 25% EtOAc in petroleum ether) to give of product **4a** (298.2 mg, 83%) as a white solid, m.p. = 155–157 °C (*R*_f = 0.3 in 1 : 3 v/v ethyl acetate/60–90 petroleum ether). ¹H NMR (400 MHz, CDCl₃) δ 8.94 (s, 1H), 8.80 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 7.2 Hz, 2H), 6.95 (t, *J* = 6.8 Hz, 1H), 4.48–4.43 (m, 2H), 2.37 (s, 3H), 1.44 (t, *J* = 7.2, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.4, 149.0, 146.0, 144.2, 136.8, 129.4 (2C), 128.5, 128.2 (2C), 127.9, 117.0, 114.1, 100.3, 61.0, 21.6, 14.7; IR (KBr) ν 3257, 2308, 1656, 1550, 1435, 1336, 1220, 1165, 1089 cm⁻¹; HRMS (ESI-TOF) (*m/z*). Calcd for C₁₇H₁₇N₃O₄S, [*M* + H]⁺ 360.1013, found 360.1006.

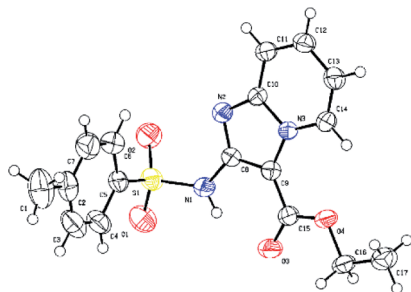


Fig. 2 Single-crystal X-ray analysis of **4a** (CCDC 2121234).†



The products 4b–4x were prepared by the similar procedure

Ethyl-8-methyl-2-((4-methylphenyl)sulfonamido)imidazo[1,2-*a*]pyridine-3-carboxylate (**4b**) (242.7 mg, 65%), white solid, m.p. = 151–152 °C (R_f = 0.25 in 1 : 4 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, CDCl_3) δ 8.78 (s, 1H), 8.68 (s, 1H), 8.14 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 6.8 Hz, 1H), 6.83 (t, J = 6.8 Hz, 1H), 4.40–4.46 (m, 2H), 2.55 (s, 3H), 2.37 (s, 3H), 1.43 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.6, 148.4, 146.0, 144.2, 136.7, 129.1 (2C), 128.9 (2C), 127.6, 126.7, 125.6, 113.9, 100.5, 60.9, 21.7, 16.7, 14.7; IR (KBr) ν 2974, 1654, 1544, 1446, 1359, 1236, 1163, 1087, 1056 cm^{-1} ; HRMS (ESI) (m/z). Calcd for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_4\text{S}$, $[\text{M} + \text{H}]^+$ 374.1169, found 374.1162.

Ethyl-7-ethyl-2-((4-methylphenyl)sulfonamido)imidazo[1,2-*a*]pyridine-3-carboxylate (**4c**) (333.0 mg, 86%), yellow solid, m.p. = 109–111 °C (R_f = 0.33 in 1 : 3 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, CDCl_3) δ 8.81 (s, 2H), 8.06 (d, J = 7.6 Hz, 2H), 7.39 (s, 1H), 7.27 (d, J = 7.6 Hz, 2H), 6.80 (d, J = 6.8 Hz, 1H), 4.46–4.41 (m, 2H), 2.72–2.67 (m, 2H), 2.37 (s, 3H), 1.43 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.5, 148.8, 146.5, 144.2, 136.8, 129.5 (3C), 128.1 (2C), 127.3, 115.7, 114.4, 100.2, 61.0, 28.5, 21.7, 14.7, 14.2; IR (KBr) ν 2970, 1656, 1544, 1436, 1384, 1220, 1165, 1085, 864 cm^{-1} ; HRMS (ESI) (m/z). Calcd for $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_4\text{S}$, $[\text{M} + \text{H}]^+$ 388.1326, found 388.1326.

Ethyl-5-ethyl-2-((4-methylphenyl)sulfonamido)imidazo[1,2-*a*]pyridine-3-carboxylate (**4d**) (89.5 mg, 23%), yellow solid, m.p. = 105–107 °C (R_f = 0.25 in 1 : 4 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, CDCl_3) δ 8.84 (s, 1H), 8.05 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.8 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.27 (d, J = 7.2 Hz, 2H), 6.80 (d, J = 6.8 Hz, 1H), 4.43–4.38 (m, 2H), 3.13–3.07 (m, 2H), 2.37 (s, 3H), 1.43 (t, J = 6.8 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.7, 150.1, 148.3, 145.3, 144.1, 136.8, 129.5, 129.4 (2C), 128.3 (2C), 114.6, 113.5, 101.9, 61.3, 27.4, 21.7, 14.7, 11.3; IR (KBr) ν 3263, 2978, 1597, 1519, 1440, 1327, 1159, 1089, 812, 663 cm^{-1} ; HRMS (ESI) (m/z). Calcd for $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_4\text{S}$, $[\text{M} + \text{H}]^+$ 388.1326, found 388.1317.

Ethyl-8-methoxy-2-((4-methylphenyl)sulfonamido)imidazo[1,2-*a*]pyridine-3-carboxylate (**4e**) (202.4 mg, 52%), white solid, m.p. = 162–164 °C (R_f = 0.25 in 1 : 3 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, CDCl_3) δ 8.69 (s, 1H), 8.57 (d, J = 6.4 Hz, 1H), 8.11 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.83 (t, J = 7.4 Hz, 1H), 6.70 (d, J = 7.6 Hz, 1H), 4.46–4.41 (m, 2H), 3.99 (s, 3H), 2.37 (s, 3H), 1.43 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.6, 148.3, 148.0, 144.2, 139.9, 137.0, 129.4 (2C), 128.6 (2C), 120.6, 114.1, 106.5, 101.4, 61.1, 56.5, 21.8, 14.7; IR (KBr) ν 2983, 1656, 1544, 1452, 1267, 1159, 1089, 1012, 665 cm^{-1} ; HRMS (ESI) (m/z). Calcd for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_5\text{S}$, $[\text{M} + \text{H}]^+$ 390.1118, found 390.1112.

Ethyl-2-(phenylsulfonamido)imidazo[1,2-*a*]pyridine-3-carboxylate (**4f**) (303.8 mg, 88%), white solid, m.p. = 116–118 °C (R_f = 0.25 in 1 : 3 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, CDCl_3) δ 8.93 (s, 2H), 8.19 (d, J = 7.6 Hz, 2H), 7.59 (d, J = 8.8 Hz, 1H), 7.54 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.4 Hz, 2H), 7.37 (t, J = 8.0 Hz, 1H), 6.95 (t, J = 6.8 Hz, 1H), 4.48–4.42 (m,

2H), 1.44 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.5, 149.0, 145.9, 139.7, 133.3, 128.8 (2C), 128.6, 128.2 (2C), 127.9, 117.0, 114.1, 100.3, 61.0, 14.7; IR (KBr) ν 3273, 2983, 1660, 1546, 1440, 1332, 1220, 1166, 1087 cm^{-1} ; HRMS (ESI) (m/z). Calcd for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_4\text{S}$, $[\text{M} + \text{H}]^+$ 346.0856, found 346.0851.

Ethyl-2-((4-chlorophenyl)sulfonamido)imidazo[1,2-*a*]pyridine-3-carboxylate (**4g**) (292.4 mg, 77%), white solid, m.p. = 141–143 °C (R_f = 0.3 in 1 : 3 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, CDCl_3) δ 8.94 (s, 2H), 8.15 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 9.2 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.40 (t, J = 8.0 Hz, 1H), 6.97 (t, J = 6.6 Hz, 1H), 4.49–4.44 (m, 2H), 1.45 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.5, 148.8, 145.9, 139.8, 138.2, 129.8 (2C), 129.1 (2C), 128.7, 127.9, 117.0, 114.3, 100.4, 61.1, 14.7; IR (KBr) ν 3273, 2981, 1660, 1546, 1438, 1334, 1219, 1166, 1082 cm^{-1} ; HRMS (ESI) (m/z). Calcd for $\text{C}_{16}\text{H}_{14}\text{ClN}_3\text{O}_4\text{S}$, $[\text{M} + \text{H}]^+$ 380.0467, found 380.0460.

Ethyl-2-((4-bromophenyl)sulfonamido)imidazo[1,2-*a*]pyridine-3-carboxylate (**4h**) (318.2 mg, 75%), white solid, m.p. = 135–137 °C (R_f = 0.3 in 1 : 4 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, CDCl_3) δ 8.94 (s, 2H), 8.07 (d, J = 8.0 Hz, 2H), 7.61 (t, J = 8.2 Hz, 3H), 7.40 (t, J = 7.8 Hz, 1H), 6.98 (t, J = 6.6 Hz, 1H), 4.49–4.44 (m, 2H), 1.45 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.5, 148.6, 143.9, 138.8, 132.1 (2C), 129.9 (2C), 128.7, 128.4, 127.9, 117.0, 114.3, 100.4, 61.2, 14.7; IR (KBr) ν 2964, 1658, 1546, 1438, 1330, 1217, 1147, 1085, 873, 759 cm^{-1} ; HRMS (ESI) (m/z). Calcd for $\text{C}_{16}\text{H}_{14}\text{BrN}_3\text{O}_4\text{S}$, $[\text{M} - \text{H}]^-$ 421.9815, found 421.9816.

Ethyl-2-((4-(trifluoromethyl)phenyl)sulfonamido)imidazo[1,2-*a*]pyridine-3-carboxylate (**4i**) (272.8 mg, 66%), yellow solid, m.p. = 160–162 °C (R_f = 0.25 in 1 : 3 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, CDCl_3) δ 8.94 (d, J = 6.4 Hz, 1H), 8.34 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.8 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.00 (t, J = 6.6 Hz, 1H), 4.50–4.45 (m, 2H), 1.46 (t, J = 7.0 Hz, 3H) (N–H signals obscured); ^{13}C NMR (100 MHz, CDCl_3) δ 160.5, 148.5, 145.8, 143.2, 135.0 (q, J = 32.8 Hz, 1C), 129.0, 128.8 (2C), 128.0, 126.0 (q, J = 3.8 Hz, 2C), 121.9 (q, J = 271.3 Hz, 1C), 117.0, 114.5, 100.6, 61.3, 14.7; IR (KBr) ν 3273, 2985, 1664, 1546, 1438, 1321, 1166, 1128, 1087, 1060 cm^{-1} ; HRMS (ESI) (m/z). Calcd for $\text{C}_{17}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_4\text{S}$, $[\text{M} + \text{H}]^+$ 414.0730, found 414.0730.

Ethyl-2-((4-methoxyphenyl)sulfonamido)imidazo[1,2-*a*]pyridine-3-carboxylate (**4j**) (217.6 mg, 58%), yellow solid, m.p. = 135–137 °C (R_f = 0.3 in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, CDCl_3) δ 8.95 (s, 1H), 8.79 (s, 1H), 8.12 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.8 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 6.97–6.92 (m, 3H), 4.48–4.43 (m, 2H), 3.82 (s, 3H), 1.44 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.4, 160.5, 149.0, 146.0, 131.3, 130.5 (2C), 128.5, 127.9, 117.0, 114.1, 113.9 (2C), 100.3, 61.0, 55.6, 14.7; IR (KBr) ν 3363, 1685, 1546, 1442, 1325, 1219, 1159, 1085, 773 cm^{-1} ; HRMS (ESI) (m/z). Calcd for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_5\text{S}$, $[\text{M} + \text{H}]^+$ 376.0962, found 376.0956.

Ethyl-2-(methylsulfonamido)imidazo[1,2-*a*]pyridine-3-carboxylate (**4k**) (172.8 mg, 61%), yellow solid, m.p. = 145–147 °C (R_f = 0.22 in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, CDCl_3) δ 9.05 (s, 1H), 8.49 (s, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.02 (t, J = 7.0 Hz, 1H), 4.50–4.45 (m, 2H), 3.51 (s, 3H), 1.46 (t, J = 7.0 Hz, 3H); ^{13}C



NMR (100 MHz, CDCl₃) δ 160.3, 149.1, 146.0, 128.9, 128.0, 116.8, 114.3, 100.3, 61.1, 42.1, 14.7; IR (KBr) ν 3294, 2983, 1662, 1546, 1438, 1328, 1219, 1153, 1085, 758 cm⁻¹; HRMS (ESI) (*m/z*). Calcd for C₁₁H₁₃N₃O₄S, [M + H]⁺ 284.0700, found 284.0693.

Ethyl-2-(ethylsulfonamido)imidazo[1,2-*a*]pyridine-3-carboxylate (**4l**) (193.2 mg, 65%), brown solid, m.p. = 114–116 °C (*R*_f = 0.20 in 1 : 4 v/v ethyl acetate/60–90 petroleum ether). ¹H NMR (400 MHz, CDCl₃) δ 9.05 (s, 1H), 8.37 (s, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.02 (t, *J* = 6.8 Hz, 1H), 4.51–4.46 (m, 2H), 3.75–3.69 (m, 2H), 1.47–1.43 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 160.4, 149.3, 146.0, 128.8, 128.0, 116.8, 114.3, 100.3, 61.1, 48.2, 14.7, 8.2; IR (KBr) ν 3363, 1685, 1546, 1440, 1325, 1219, 1157, 1085, 773 cm⁻¹; HRMS (ESI) (*m/z*). Calcd for C₁₂H₁₅N₃O₄S, [M + H]⁺ 298.0856, found 298.0850.

Ethyl-2-(propylsulfonamido)imidazo[1,2-*a*]pyridine-3-carboxylate (**4m**) (236.5 mg, 76%), white solid, m.p. = 129–130 °C (*R*_f = 0.30 in 1 : 4 v/v ethyl acetate/60–90 petroleum ether). ¹H NMR (400 MHz, CDCl₃) δ 9.04 (s, 1H), 8.40 (s, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.01 (t, *J* = 6.8 Hz, 1H), 4.50–4.44 (m, 2H), 3.66 (t, *J* = 7.8 Hz, 2H), 1.99–1.90 (m, 2H), 1.45 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.3, 149.2, 146.0, 128.8, 128.0, 116.8, 114.2, 100.2, 61.1, 55.4, 17.2, 14.2, 12.9; IR (KBr) ν 3363, 1685, 1544, 1440, 1365, 1325, 1274, 1219, 1157, 1085 cm⁻¹; HRMS (ESI) (*m/z*). Calcd for C₁₃H₁₇N₃O₄S, [M + H]⁺ 312.1013, found 312.1006.

Ethyl-2-((2-methylpropyl)sulfonamido)imidazo[1,2-*a*]pyridine-3-carboxylate (**4n**) (214.6 mg, 66%), white solid, m.p. = 114–116 °C (*R*_f = 0.30 in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.30 (s, 1H), 9.10 (d, *J* = 6.8 Hz, 1H), 7.71 (d, *J* = 9.2 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 6.8 Hz, 1H), 4.41–4.36 (m, 2H), 3.57 (d, *J* = 6.4 Hz, 2H), 2.29–2.19 (m, 1H), 1.36 (t, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 6H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 159.8, 147.8, 144.8, 129.3, 127.8, 116.2, 114.7, 101.0, 60.6, 60.4, 24.2, 22.1 (2C), 14.3; IR (KBr) ν 2964, 1658, 1546, 1438, 1330, 1217, 1147, 1085 cm⁻¹; HRMS (ESI) (*m/z*). Calcd for C₁₄H₁₉N₃O₄S, [M + H]⁺ 326.1169, found 326.1163.

Methyl-2-((4-methylphenyl)sulfonamido)imidazo[1,2-*a*]pyridine-3-carboxylate (**4o**) (276.2 mg, 80%), white solid, m.p. = 144–146 °C (*R*_f = 0.30 in 1 : 5 v/v ethyl acetate/60–90 petroleum ether). ¹H NMR (400 MHz, CDCl₃) δ 8.90 (s, 1H), 8.69 (s, 1H), 8.03 (d, *J* = 7.6 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 2H), 6.90 (t, *J* = 7.0 Hz, 1H), 3.93 (s, 3H), 2.32 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.7, 149.0, 146.0, 144.2, 136.8, 129.4 (2C), 128.6, 128.3 (2C), 127.9, 117.0, 114.1, 100.2, 51.8, 21.6; IR (KBr) ν 3282, 2954, 1691, 1664, 1544, 1450, 1332, 1222, 1163, 1085 cm⁻¹; HRMS (ESI) (*m/z*). Calcd for C₁₆H₁₅N₃O₄S, [M + H]⁺ 346.0856, found 346.0850.

Tert-butyl 2-((4-methylphenyl)sulfonamido)imidazo[1,2-*a*]pyridine-3-carboxylate (**4p**) (329.3 mg, 85%), white solid, m.p. = 145–147 °C (*R*_f = 0.25 in 1 : 6 v/v ethyl acetate/60–90 petroleum ether). ¹H NMR (400 MHz, CDCl₃) δ 8.87 (s, 2H), 8.01 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 9.2 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.88 (t, *J* = 6.8 Hz, 1H), 2.32 (s, 3H), 1.60 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 160.1, 148.7, 145.7, 144.1, 137.0, 129.8, 129.5 (2C), 128.2 (2C), 127.7, 117.0, 113.9, 101.2,

83.4, 28.7 (3C), 21.7; IR (KBr) ν 2978, 1658, 1544, 1438, 1334, 1263, 1165, 1085 cm⁻¹; HRMS (ESI) (*m/z*). Calcd for C₁₉H₂₁N₃O₄S, [M + H]⁺ 388.1326, found 388.1317.

N-(3-acetylimidazo[1,2-*a*]pyridin-2-yl)-4-methylbenzene sulfonamide (**4q**) (256.8 mg, 78%), yellow solid, m.p. = 176–178 °C (*R*_f = 0.25 in 1 : 1 v/v ethyl acetate/60–90 petroleum ether). ¹H NMR (400 MHz, CDCl₃) δ 9.36 (d, *J* = 7.2 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 2H), 7.86 (t, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.41 (s, 1H), 7.27 (d, *J* = 7.6 Hz, 3H), 2.54 (s, 3H), 2.39 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.5, 152.0, 149.5, 142.5, 140.0, 137.0, 129.3 (2C), 128.5, 126.6 (2C), 126.4, 117.3, 103.2, 25.1, 21.5; IR (KBr) ν 3051, 1598, 1552, 1513, 1261, 1139, 1080, 827 cm⁻¹; HRMS (ESI) (*m/z*). Calcd for C₁₆H₁₅N₃O₃S, [M + H]⁺ 330.0907, found 330.0902.

N-(3-Hexanoylimidazo[1,2-*a*]pyridin-2-yl)-4-methylbenzene sulfonamide (**4r**) (273.6 mg, 71%), brown solid, m.p. = 112–114 °C (*R*_f = 0.25 in 1 : 1 v/v ethyl acetate/60–90 petroleum ether). ¹H NMR (400 MHz, CDCl₃) δ 9.39 (d, *J* = 7.2 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 2H), 7.84 (t, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.39 (s, 1H), 7.27 (d, *J* = 7.2 Hz, 3H), 2.74 (t, *J* = 7.6 Hz, 2H), 2.39 (s, 3H), 1.76–1.67 (m, 2H), 1.32 (s, 4H), 0.89 (t, *J* = 6.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.4, 152.2, 149.6, 142.5, 140.0, 136.8, 129.3 (2C), 128.6, 126.7 (2C), 126.6, 117.2, 102.7, 38.7, 31.5, 28.4, 22.5, 21.6, 14.0; IR (KBr) ν 3118, 2926, 1598, 1550, 1415, 1280, 1139, 1080 cm⁻¹; HRMS (ESI) (*m/z*). Calcd for C₂₀H₂₃N₃O₃S, [M + H]⁺ 386.1533, found 386.1525.

Ethyl-3-((6-methylpyridin-2-yl)amino)-3-(tosylimino)propanoate (**4s**) (93.9 mg, 25%), yellow solid, m.p. = 149–151 °C (*R*_f = 0.25 in 1 : 4 v/v ethyl acetate/60–90 petroleum ether). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.94 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.73–7.68 (m, 3H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.06 (d, *J* = 7.2 Hz, 1H), 4.11–4.06 (m, 2H), 4.02 (s, 2H), 2.41 (s, 3H), 2.36 (s, 3H), 1.17 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 166.8, 158.3, 156.9, 150.0, 142.4, 139.9, 138.6, 129.4 (3C), 125.9 (2C), 120.2, 112.3, 60.9, 23.4, 20.9, 13.9; IR (KBr) ν 3286, 2983, 1737, 1597, 1541, 1452, 1280, 1145, 1087 cm⁻¹; HRMS (ESI) (*m/z*). Calcd for C₁₈H₂₁N₃O₄S, [M + H]⁺ 376.1326, found 376.1319.

Ethyl-3-((6-methoxypyridin-2-yl)amino)-3-(tosylimino)propanoate (**4t**) (234.6 mg, 60%), white solid, m.p. = 123–125 °C (*R*_f = 0.25 in 1 : 4 v/v ethyl acetate/60–90 petroleum ether). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.74 (s, 1H), 7.71 (t, *J* = 9.2 Hz, 3H), 7.63 (d, *J* = 6.8 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 2H), 6.61 (d, *J* = 7.6 Hz, 1H), 4.12–4.05 (m, 4H), 3.83 (s, 3H), 2.37 (s, 3H), 1.18 (t, *J* = 6.0 Hz, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 166.9, 162.3, 158.3, 148.4, 142.5, 141.1, 139.8, 129.4 (3C), 126.0 (2C), 107.5, 106.9, 60.9, 53.2, 20.9, 13.9; IR (KBr) ν 3288, 2983, 1739, 1597, 1543, 1463, 1423, 1145, 1089, 1024 cm⁻¹; HRMS (ESI) (*m/z*). Calcd for C₁₈H₂₁N₃O₅S, [M + H]⁺ 392.1275, found 392.1268.

4-Methyl-*N*-(3-(*m*-tolyl)imidazo[1,2-*a*]pyridin-2-yl)benzene sulfonamide (**4u**) (98.0 mg, 26%), brown solid, m.p. = 192–194 °C (*R*_f = 0.25 in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.74 (s, 1H), 8.09–8.03 (m, 2H), 7.66 (d, *J* = 7.2 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.26–7.25 (m, 3H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.02 (t, *J* = 6.4 Hz, 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.90 (s, 1H), 2.34 (s, 3H), 2.24 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 178.0, 162.5, 146.5, 141.4, 140.1, 138.0, 137.5, 135.4, 130.1, 128.62, 128.60 (2C), 126.9 (2C), 125.3,



122.1, 116.1, 115.7, 95.9, 21.0, 20.9; IR (KBr) ν 3057, 1747, 1566, 1467, 1336, 1278, 1145, 1082 cm^{-1} ; HRMS (ESI) (m/z). Calcd for $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}_2\text{S}$, $[\text{M} + \text{H}]^+$ 378.1271, found 378.1267.

N-(Pyridin-2-yl)-2-(*m*-tolyl)-*N'*-tosylacetimidamide (**4v**) (141.2 mg, 37%), yellow solid, m.p. = 103–105 °C (R_f = 0.3 in 1 : 4 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 2H), 7.90 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 7.6 Hz, 2H), 7.32–7.26 (m, 3H), 7.15–6.99 (m, 4H), 4.42 (s, 2H), 2.43 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.8, 150.2, 147.9, 142.9, 140.0, 139.5, 138.4, 132.5, 130.8, 129.6, 129.5 (2C), 129.3, 127.1, 126.6 (2C), 120.8, 115.4, 40.5, 21.6, 21.4; IR (KBr) ν 3358, 3278, 1597, 1566, 1527, 1435, 1280, 1143, 1085 cm^{-1} ; HRMS (ESI) (m/z). Calcd for $\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$, $[\text{M} + \text{H}]^+$ 380.1427, found 380.1421.

2-(4-Methoxyphenyl)-*N*-(pyridin-2-yl)-*N'*-tosylacetimidamide (**4x**) (130.5 mg, 33%), yellow solid, m.p. = 137–139 °C (R_f = 0.3 in 1 : 2 v/v ethyl acetate/60–90 petroleum ether). ^1H NMR (400 MHz, CDCl_3) δ 8.17 (s, 1H), 8.11 (s, 1H), 7.90 (d, J = 7.6 Hz, 2H), 7.60 (t, J = 8.0 Hz, 1H), 7.50 (s, 1H), 7.32 (d, J = 7.6 Hz, 2H), 7.24 (t, J = 7.0 Hz, 2H), 7.01 (t, J = 5.8 Hz, 1H), 6.94 (d, J = 6.8 Hz, 2H), 4.42 (s, 2H), 3.81 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.2, 159.7, 150.2, 148.0, 142.9, 140.0, 138.4, 131.5, 129.5 (3C), 126.6 (3C), 124.2, 120.9, 115.3, 115.2, 55.4, 39.9, 21.6; IR (KBr) ν 3358, 2837, 1597, 1512, 1433, 1247, 1143, 1085 cm^{-1} ; HRMS (ESI) (m/z). Calcd for $\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_3\text{S}$, $[\text{M} + \text{H}]^+$ 396.1377, found 396.1369.

All NMR spectra please see ESI Section 3.†

Conflicts of interest

There are no conflicts to declare.

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