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Synthesis of Imidazoheterocycle-Hydrazine, -Carbamate, and Imidazocinnoline Derivatives

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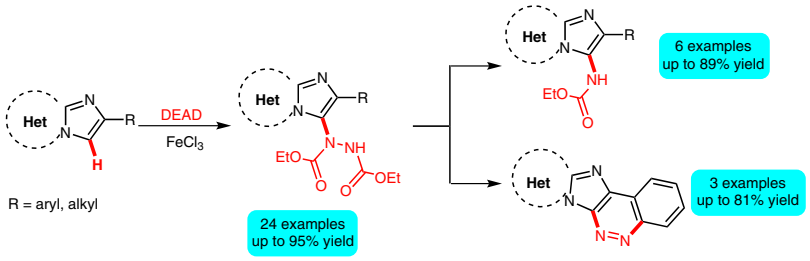

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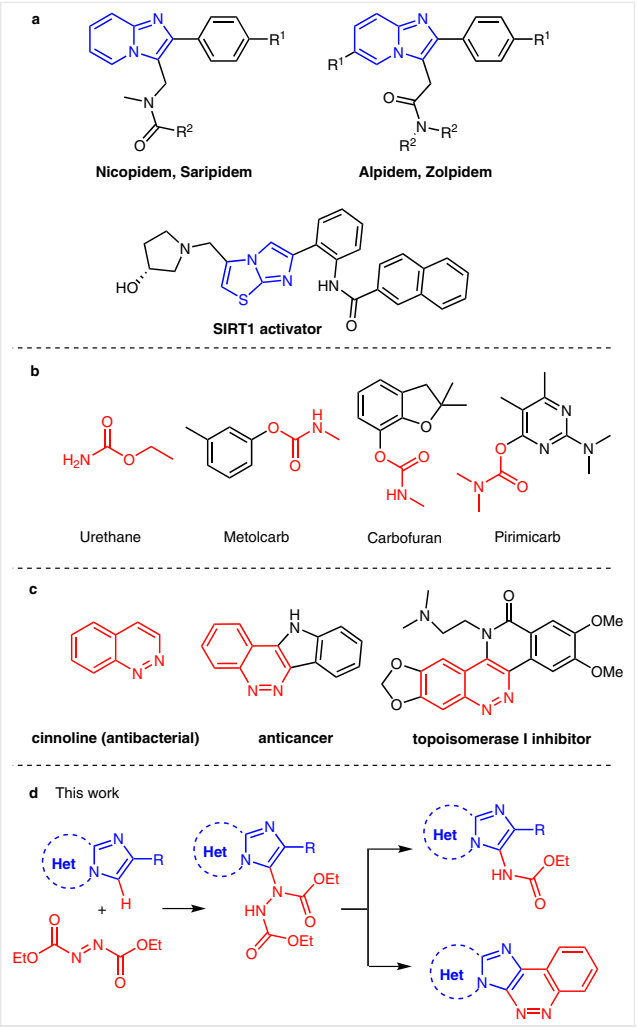
Abstract Iron-catalyzed amination of imidazoheterocycles with diethyl azodicarboxylate (DEAD) under mild conditions has been developed. This strategy tolerates a wide range of functional groups to afford diverse imidazoheterocycle-hydrazines in moderate to excellent yields. Significantly, imidazoheterocycle hydrazines can be converted into imidazoheterocycle carbamates and imidazocinnolines.

Key words iron, amination, imidazoheterocycle, carbamate, cinnoline

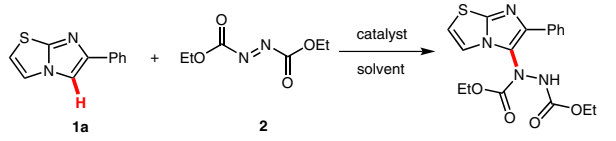
Imidazoheterocycles are a class of important drug skeleton with a broad range of biological activities.[1] Many drugs such as saripidem, nicopidem, alpidem, zolpidem, and SIRT1 activator have been developed from imidazoheterocycles (Scheme 1, a).[2] In recent years, increasing attention has been paid to the diversity synthesis of imidazoheterocycles.[3] Direct introduction of pharmacophores onto imidazoheterocycles is particularly interesting because it is an effective way to engineer bioactive molecules for drug discovery.[4–16] These reaction techniques include thiolation,[4] thiocyanation,[5] dithiocarbamation,[6] phosphonation,[7] nitrosation,[8] amination,[9] carbonylation,[10] trifluoromethylation,[11] trifluoromethylthiolation,[12] fluorination,[13] heteroarylation,[14] alkenylation,[15] and alkylation.[16] Although great progress has been achieved, there is still an intrinsic need to introduce novel pharmacophores onto imidazoheterocycles for drug development. Very recently, we have successfully carried out the dithiocarbamation of imidazoheterocycles.[6] However, the introduction of carbamate onto imidazoheterocycles has not yet been developed. In addition, although some efforts have been devoted to the synthesis of several heterocycle-fused imidazopyridines,[17] the synthesis of cinnoline-fused imidazoheterocycles is not yet reported. It is reported that the carbamate motif can be derived from the cleavage of N–N bond of diethyl azodicarboxylate (DEAD).[18] It is also reported that bipheylhydrazine-1,2-dicarboxylates can undergo a cyclization to produce benzocinnoline.[19] Inspired by these works, we envisioned synthesizing imidazoheterocycle-carbamates and imidazocinnolines from imidazoheterocycle-hydrazines (Scheme 1, d). As well known, carbamate is a significant structural unit, which is prevalent in medicinal and agricultural chemicals (such as urethane, Metolcarb, Carbofuran and Pirimicarb) (Scheme 1, b).[20] As for cinnoline, it has been considered as a privileged scaffold in medicinal chemistry due to its promising anticancer activities (Scheme 1, c).[21] Additionally, fused cinnolines have also been applied in organic nonlinear optic (NLO) materials by utilizing a polarized heteroaromatic π-system.[22] Therefore, it is highly necessary to explore efficient synthetic methods for imidazoheterocycle-hydrazines, -carbamates, and imidazocinnolines. Herein, we report an iron-catalyzed method for the synthesis of imidazoheterocycle-hydrazines, which can be further transformed to imidazoheterocycle-carbamates and imidazocinnolines (Scheme 1, d).

The reaction between 6-phenylimidazo[2,1-*b*]thiazole (**1a**) and DEAD (**2a**) was used as the reaction model, and the results are summarized in Table 1. At the outset, we reasoned that the addition of Lewis acid may favor the amination addition of **1a** with DEAD. Thus several Lewis acids such as $PdCl_2$, $AlCl_3$, $FeCl_3$, and $ZnCl_2$ were evaluated in DMSO at 80 °C for 12 hours (Table 1, entries 1–4). $FeCl_3$, as an ecofriendly reagent, was proved to be the most effective, giving the target product **3** in 81% yield (entry 3). Next, various solvents, including NMP, DMA, MeCN, EtOH, DCE, toluene, and 1,4-dioxane, were investigated in the presence of 10 mol% of $FeCl_3$ at 80 °C (entries 5–11). MeCN is a preferable solvent for the amination, giving product **3** in 93% yield (entry 7). Encouraged by this result, we attempted lowering



Scheme 1 Biological molecules for imidazoheterocycles, carbamates, and cinnolines

Table 1 Screening of Optimal Conditions[a]



Entry	Cat. (mol %)	Solvent	Temp (°C)	Isolated yield (%)
1	$PdCl_2$ (10)	DMSO	80	79
2	$AlCl_3$ (10)	DMSO	80	72
3	$FeCl_3$ (10)	DMSO	80	81
4	$ZnCl_2$ (10)	DMSO	80	55
5	$FeCl_3$ (10)	NMP	80	32
6	$FeCl_3$ (10)	DMA	80	66
7	$FeCl_3$ (10)	MeCN	80	93
8	$FeCl_3$ (10)	EtOH	80	37
9	$FeCl_3$ (10)	DCE	80	13
10	$FeCl_3$ (10)	1,4-dioxane	80	76
11	$FeCl_3$ (10)	toluene	80	72
12	$FeCl_3$ (5)	MeCN	80	84
13	–	MeCN	80	65
14	$FeCl_3$ (10)	MeCN	60	66
15	$FeCl_3$ (10)	MeCN	r.t.	32

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), solvent (2 mL), reaction time 12 h.

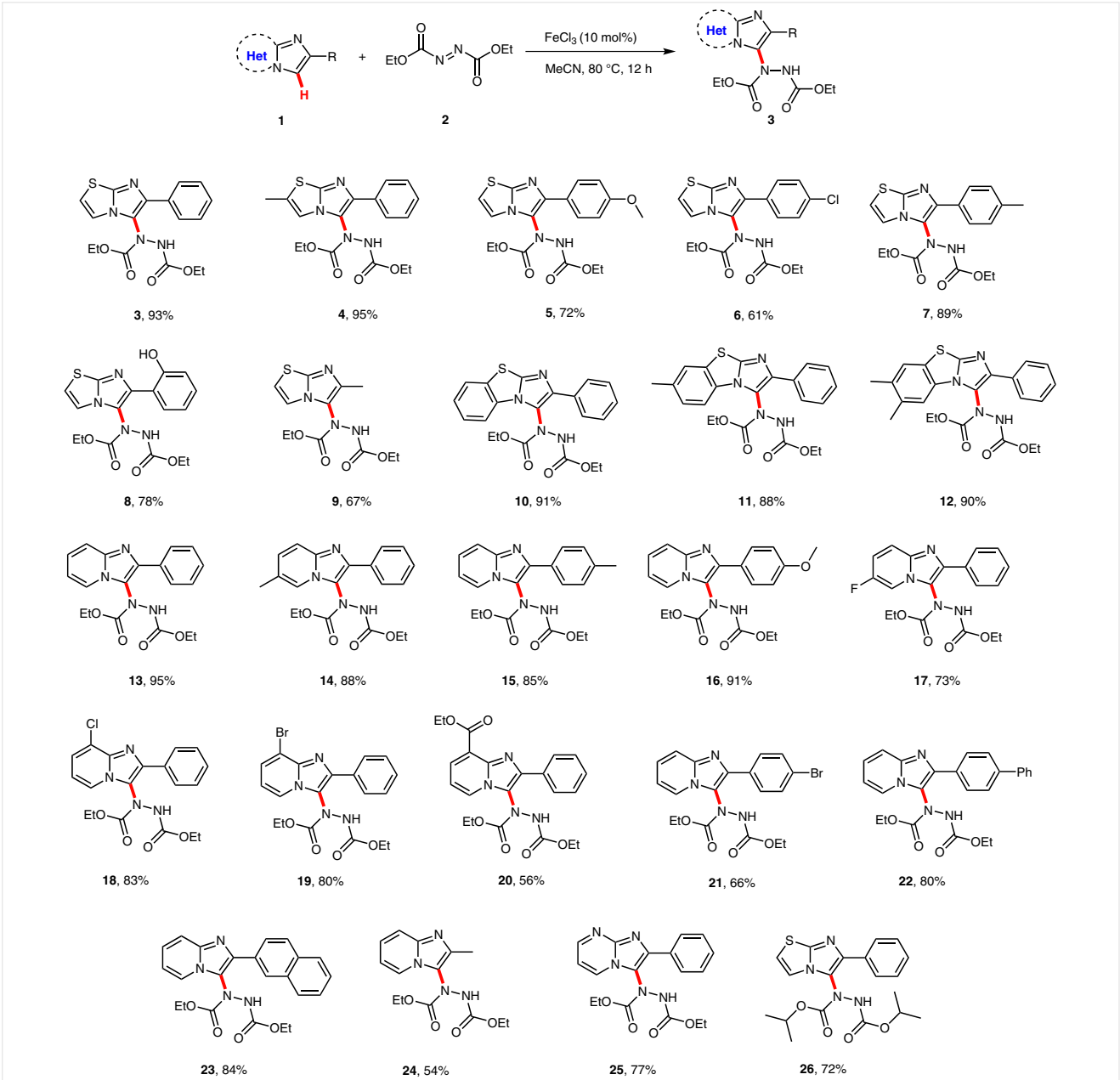
the loading of $FeCl_3$ to obtain a desirable yield (entry 12). It was shown that the amination still proceeded well with an 84% yield of product **3** in the presence of 5 mol% of $FeCl_3$. On the contrary, the yield of **3** was reduced to 65% when the reaction was conducted in the absence of $FeCl_3$ (entry 13).[9] These results suggest that Lewis acid indeed accelerate the amination. Further study shows that the reaction is highly dependent on the temperature. The reaction at 60 °C gave product **3** only in 66% yield in the presence of 10 mol% of $FeCl_3$ (entry 14), and the yield was sharply reduced to 32% when the reaction was conducted at room temperature (entry 15).

With the optimized reaction conditions in hand (Table 1, entry 7), the scope and generality of imidazoheterocycles were investigated (Scheme 2). Imidazothiazole with a methyl on the thiazole ring was tolerated well under the standard conditions to give product **4** in 95% yield. To our delight, the substrate with a hydroxyl group on the benzene ring also performed well to give product **8** in 78% yield. By comparison with 6-phenylimidazo[2,1-*b*]thiazole, 6-methylimidazo[2,1-*b*]thiazole was less reactive in the amination, only a 67% yield of product **9** was obtained. It may result from the conjugation effect between benzene ring and imidazole ring, which can stabilize the imidazole ring to favor the reaction, whereas the methyl group has no conjugation effect with the imidazole ring, leading to a lower yield. It was pleasing to find that imidazo[2,1-*b*]benzothiazoles also underwent the amination smoothly to give products **10**–**12** in good yields.

Next, the scope of imidazo[2,1-*b*]pyridines was also investigated (products **13**–**24**). 2-Phenylimidazo[1,2-*a*]pyridine appears to have excellent reactivity to give product **13** in 95% yield. Generally, the substrates with an electron-donating group have better reactivity than those with an electron-withdrawing group. For example, the substrate with a methoxy group gave product **16** in 91% yield, whereas the substrate with a fluoro group provided product **17** in 73% yield. The reaction of halo-substituted substrates (including fluorine, chlorine, bromine, and ester) proceeded well to give the corresponding products in moderate to good yields (products **17**–**21**). It is noteworthy that both products **18** and **19** are synthetically useful for further

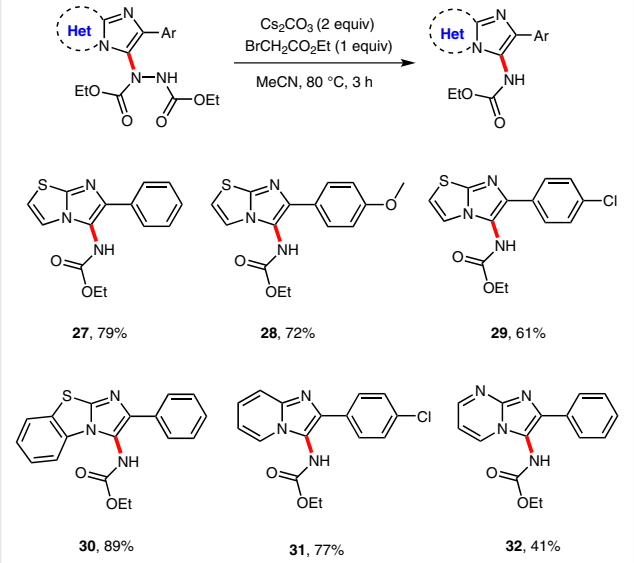
modification by coupling reaction at the halo group. The substrate with an ester group also performed well to give product **20** in 56% yield. The substrates with a biphenyl or a naphthyl group were also tolerated well under the standard conditions, giving products **22** and **23** in 80% and 84% yield, respectively. Because of the poor reactivity, 2-methylimidazo[1,2-*a*]pyridine gave only product **24** in 54% yield. To our delight, imidazopyrimidine is also a suitable substrate for this transformation, providing the target product **25** in 77% yield. By comparison with DEAD, diisopropyl diazene-1,2-dicarboxylate showed poor reactivity in the reaction with imidazothiazole **1a**, only a 72% yield of product **26** was obtained, which may result from the steric effect of isopropyl group.

To date, direct introduction of carbamate onto heterocycles is still a challenge, which results in a slow progress in this field. We reasoned that whether imidazoheterocycle-carbamates can be prepared from imidazoheterocycle-hydrazines by the cleavage of the N–N bond in hydrazines. Based on the previous work,[18] we set out to investigate the



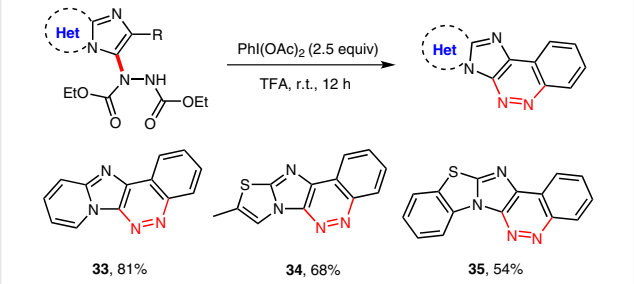
Scheme 2 The scope of amination. *Reagents and conditions*: **1** (0.2 mmol), **2** (0.3 mmol, 1.5 equiv), $FeCl_3$ (10 mol%), and MeCN (2 mL) at 80 °C for 12 h.

transformation of imidazoheterocycle-hydrazines to the corresponding carbamates. It was shown that the cleavage of the N–N bond in hydrazines proceeded smoothly in the presence of ethyl bromoacetate and Cs_2CO_3 in MeCN at 80 °C, providing imidazoheterocycle-carbamates in moderate to good yields (Scheme 3, products **27**–**32**). It was demonstrated that various imidazoheterocycles (including imidazothiazole, imidazopyridine, and imidazopyrimidine) have good tolerance in the transformation.



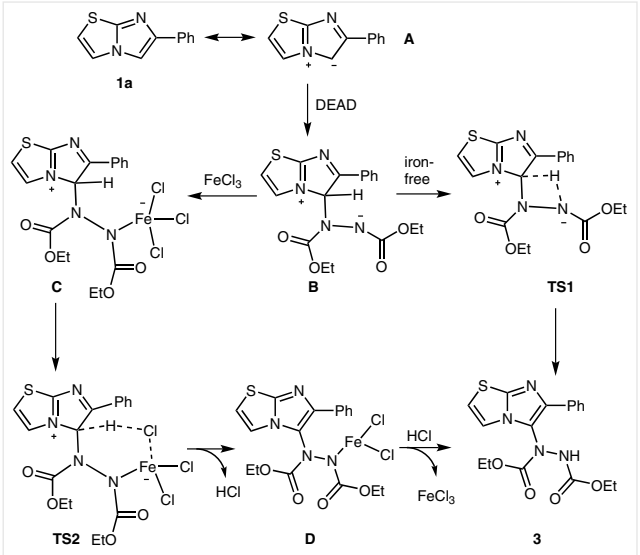
Scheme 3 Synthesis of imidazoheterocycle-carbamates. *Reagents and conditions*: imidazoheterocycle-hydrazines (0.2 mmol), Cs_2CO_3 (2 equiv), $BrCH_2CO_2Et$ (0.2 mmol, 1 equiv), in MeCN (2 mL) at 80 °C for 3 h.

Subsequently, imidazocinnolines were prepared from imidazoheterocycle-hydrazines. As shown in Scheme 4, both imidazopyridine-hydrazine and imidazothiazole-hydrazine are suitable for this oxidative cyclization, giving target product in moderate to good yields (products **33**–**35**). These fused imidazocinnolines are of great interest in the field of organic materials.



Scheme 4 Synthesis of imidazocinnolines. *Reagents and conditions*: **3** (0.2 mmol), $PhI(OAc)_2$ (2.5 equiv), and TFA (2 mL) at r.t. for 12 h.

Based on the amination results, a plausible mechanism for the current transformation is outlined in Scheme 5. Initially, substrate **1a** may have a resonance structure **A**, which undergoes a nucleophilic addition with DEAD to afford intermediate **B**. In the absence of $FeCl_3$, intermediate **B** can be further transformed into product **3** through a four-membered-ring transition state (**TS1**) under heating conditions. In the $FeCl_3$-catalyzed reaction, intermediate **B** would chelate with $FeCl_3$ to form intermediate **C**, followed by **TS2** to produce intermediate **D** with release of HCl. Finally, intermediate **D** reacts with HCl to give product **3**.



Scheme 5 Proposed mechanism

To better understand the details for the $FeCl_3$-catalyzed amination of imidazoheterocycles with DEAD, DFT calculations were performed (Figure 1). For the hydrogen atom migration step, the noncatalyzed reaction via **TS1** requires an activation free energy of 32.57 kcal/mol. Interestingly, when the nitrogen atom of amide is coordinated to $FeCl_3$, intermediate **C** is readily formed from intermediate **B** with a remarkable drop of activation free energy (–12.90 kcal/mol). At the aid of $FeCl_3$, the dehydrogenation occurs via **TS2** with a significantly reduced barrier of 6.05 kcal/mol, demonstrating that the dehydrogenation step is efficiently catalyzed by $FeCl_3$.

In summary, we have developed an iron-catalyzed strategy for the convenient synthesis of imidazoheterocycle-hydrazines from the amination of imidazoheterocycles with DEAD under mild conditions. Importantly, imidazoheterocycle-hydrazines are allowed to be further transformed to imidazoheterocycle-carbamates and imidazocinnolines. These compounds are expected to have great potential applications in medicinal and material chemistry.

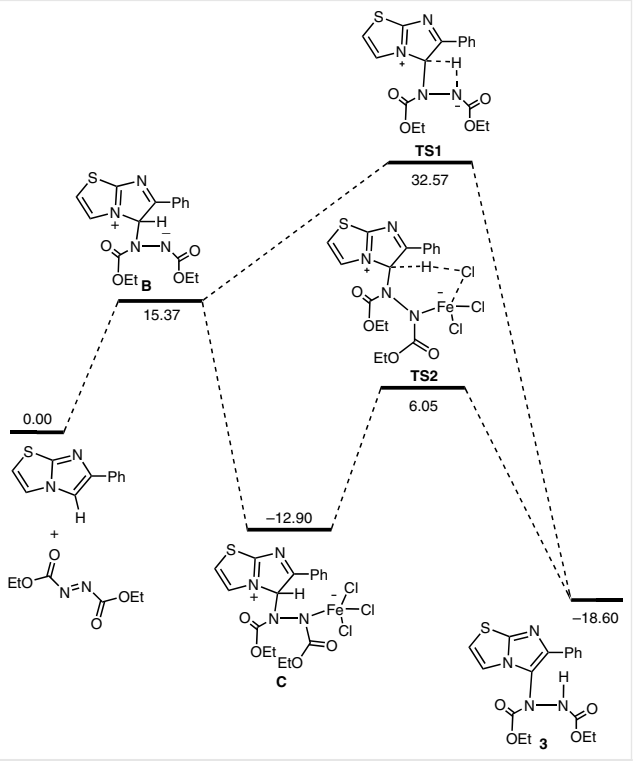


Figure 1 Free energy profile for pathways (unit: kcal/mol)

^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance III 500 instrument (500 MHz for ^{1}H, 125 MHz for ^{13}C NMR spectroscopy) using $CDCl_3$ or DMSO-d_6 as the solvent, referenced to internal TMS (0.0 ppm) as the standard. Mass spectra were measured on a Shimadzu GC-MS-QP2010 Plus spectrometer (EI). HRMS (ESI) analysis was measured on a Bruker micrOTOF-Q II instrument. IR analysis was measured on a Nicolet IS10 spectrometer (ATR).

Analytical Data for Products 3–35

Note: The phenomenon of the rotational isomerization of amides can be found in the ^{1}H NMR spectra.

Computational Details

The calculations were carried out using the Gaussian 09 programs,[23] where the Density Functional Theory on Becke's three-parameter nonlocal exchange functional along with the Lee–Yang–Parr nonlocal correlation functional (B3LYP)[24,25] was employed. The 6-31G (d) basis set was applied for all the atoms except the metal, S and Cl atoms, for which LANL2DZ basis set including a double valence basis set with the Hay and Wadt effective core potential (ECP) was used.[26,27] Besides, an additional d polarization shells were added for Cl with exponent of 0.514 and S with exponent of 0.421. The solvent effect of MeCN (experimentally used) was considered by the polarized continuum (PCM) model combined with the addition of the MeOH molecule to the calculated system.[28–30] Frequency analysis was used to confirm whether the structure is a minimum (with no imaginary frequency) or a transition state (only with one imaginary frequency) and to provide free energies at 298.15 K.

Hydrazination of Imidazoheterocycles with DEAD; Diethyl 1-(6-Phenylimidazo[2,1-*b*]thiazol-5-yl)hydrazine-1,2-dicarboxylate (3); Typical Procedure

A 15 mL tube with a Teflon cap, equipped with a magnetic stirring bar, was charged with substrate **1a** (40 mg, 0.20 mmol), DEAD (52 mg, 0.3 mmol, 1.5 equiv), and $FeCl_3$ (3 mg, 10 mol%). After the addition of MeCN (2 mL), the tube was capped and the contents were stirred at 80 °C for 12 h. After cooling to r.t., the crude mixture was diluted with EtOAc, and the EtOAc layer was washed with brine (3 × 10 mL). The combined organic phases were dried (anhyd Na_2SO_4), filtered through a Celite pad, and washed with EtOAc. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography (hexane–EtOAc) to afford product **3** as a light yellow solid.

Yield: 69.6 mg (93%); white solid; mp 123.8–125.1 °C.

IR (ATR): 3226, 2974, 1746, 1501, 1239, 1093, 760, 679 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82 (s, 1 H), 7.64 (d, *J* = 7.5 Hz, 2 H), 7.35–7.30 (m, 3 H), 7.24–7.19 (m, 1 H), 6.73 (s, 1 H), 4.20–4.03 (m, 4 H), 1.31–1.07 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.8, 155.1, 148.1, 138.4, 133.1, 128.8, 127.9, 126.3, 125.3, 119.3, 112.1, 64.0, 62.6, 14.4, 14.3.

LRMS (EI, 70 eV): *m*/*z* (%) = 374 (26), 301 (27), 214 (27), 207 (33), 187 (100).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{17}N_4O_4S$ (M – H)$^-$: 373.0965; found: 373.0969.

Diethyl 1-(2-Methyl-6-phenylimidazo[2,1-*b*]thiazol-5-yl)hydrazine-1,2-dicarboxylate (4)

Yield: 73.7 mg (95%); white solid; mp 184.6–185.7 °C.

IR (ATR): 3299, 2968, 1746, 1504, 1242, 1076, 778 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (s, 1 H), 7.61 (d, *J* = 7.5 Hz, 2 H), 7.51 (s, 1 H), 7.26 (d, *J* = 6.0 Hz, 2 H), 7.20–7.18 (m, 1 H), 4.10 (m, 4 H), 2.32 (s, 3 H), 1.12 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.9, 155.2, 147.5, 139.5, 133.2, 128.7, 127.6, 126.2, 119.7, 115.7, 111.5, 63.9, 62.5, 14.4, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}N_4O_4S$ (M – H)$^-$: 387.1121; found: 387.1148.

Diethyl 1-[6-(4-Methoxyphenyl)imidazo[2,1-*b*]thiazol-5-yl]hydrazine-1,2-dicarboxylate (5)

Yield: 58.2 mg (72%); yellow solid; mp 179.2–180.1 °C.

IR (ATR): 3228, 2914, 1755, 1504, 1245, 1056, 776, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.88 (s, 1 H), 7.65 (d, *J* = 8.0 Hz, 3 H), 6.90 (d, *J* = 8.0 Hz, 2 H), 6.77 (s, 1 H), 4.21–4.17 (m, 4 H), 3.81 (s, 3 H), 1.26–1.21 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.3, 156.9, 155.2, 148.0, 140.9, 127.6, 125.8, 119.4, 114.2, 111.7, 63.9, 62.5, 55.3, 14.4, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{21}N_4O_5S$ (M + H)$^+$: 405.1227; found: 405.1233.

Diethyl 1-[6-(4-Chlorophenyl)imidazo[2,1-*b*]thiazol-5-yl]hydrazine-1,2-dicarboxylate (6)

Yield: 49.8 mg (61%); white solid; mp 175.6–177.0 °C.

IR (ATR): 3260, 2921, 1739, 1510, 1251, 1068, 769, 650 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10 (s, 1 H), 7.84 (s, 1 H), 7.57 (d, *J* = 7.5 Hz, 2 H), 7.20 (d, *J* = 7.0 Hz, 2 H), 6.72 (s, 1 H), 4.21–4.08 (m, 4 H), 1.22–1.02 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.0, 155.1, 148.3, 139.8, 133.6, 131.5, 128.8, 127.6, 120.2, 119.5, 112.4, 64.1, 62.6, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{18}N_4O_5S$ (M + H)$^+$: 409.0732; found: 409.0732.

Diethyl 1-[6-(*p*-Tolyl)imidazo[2,1-*b*]thiazol-5-yl]hydrazine-1,2-dicarboxylate (7)

Yield: 69.1 mg (89%); yellow solid; mp 165.4–166.3 °C.

IR (ATR): 3283, 2916, 1728, 1454, 1245, 1058, 824, 761 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.88 (s, 1 H), 7.60 (d, *J* = 7.5 Hz, 2 H), 7.31–7.27 (m, 1 H), 7.21 (d, *J* = 7.5 Hz, 2 H), 6.79 (s, 1 H), 4.27–4.10 (m, 4 H), 2.37 (s, 3 H), 1.28–1.13 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.8, 155.1, 148.1, 141.0, 137.8, 130.3, 129.5, 126.1, 119.4, 111.9, 64.0, 62.6, 21.3, 14.4, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}N_4O_4S$ (M – H)$^-$: 387.1121; found: 387.1145.

Diethyl 1-[6-(2-Hydroxyphenyl)imidazo[2,1-*b*]thiazol-5-yl]hydrazine-1,2-dicarboxylate (8)

Yield: 60.8 mg (78%), yellow solid; mp 166.7–168.2 °C.

IR (ATR): 3279, 2921, 1746, 1507, 1249, 1063, 753, 673 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.93 (s, 1 H), 7.98 (s, 1 H), 7.49 (s, 1 H), 7.37 (d, *J* = 7.0 Hz, 1 H), 7.25–7.16 (m, 1 H), 7.06–6.99 (m, 1 H), 6.91–6.69 (m, 2 H), 4.19 (dd, *J* = 14.5, 7.0 Hz, 4 H), 1.29–1.13 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.0, 154.9, 146.0, 139.5, 129.6, 124.7, 119.5, 119.4, 119.2, 118.0, 116.1, 112.6, 64.2, 62.7, 62.3, 14.4, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{17}N_4O_5S$ (M – H)$^-$: 389.0914; found: 389.0930.

Diethyl 1-(6-Methylimidazo[2,1-*b*]thiazol-5-yl)hydrazine-1,2-dicarboxylate (9)

Yield: 41.8 mg (67%); yellow solid; mp 67.8–69.2 °C.

IR (ATR): 3021, 2975, 1746, 1539, 1230, 1061, 613 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78 (s, 1 H), 7.74 (s, 1 H), 6.76 (s, 1 H), 4.24–4.08 (m, 4 H), 2.22 (s, 3 H), 1.21–1.12 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.7, 154.8, 148.0, 139.3, 121.5, 119.1, 112.9, 63.9, 62.6, 14.4, 12.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 312 (39), 239 (25), 152 (34), 125 (100), 124 (21).

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{15}N_4O_4S$ (M – H)$^-$: 311.0808; found: 311.0813.

Diethyl 1-(2-Phenylbenzo[*d*]imidazo[2,1-*b*]thiazol-3-yl)hydrazine-1,2-dicarboxylate (10)

Yield: 77.0 mg (91%); white solid; mp 159.6–161.1 °C.

IR (ATR): 3312, 2988, 1726, 1514, 1232, 1050, 736 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.25 (s, 1 H), 7.69 (t, *J* = 7.5 Hz, 3 H), 7.50–7.44 (m, 3 H), 7.35 (t, *J* = 7.5 Hz, 2 H), 7.18 (s, 1 H), 4.47–4.04 (m, 4 H), 1.34–1.03 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.7, 155.4, 146.6, 140.3, 133.0, 132.5, 129.9, 129.4, 129.2, 128.2, 126.2, 125.0, 123.7, 122.3, 115.4, 64.3, 62.5, 14.5, 14.3.

LRMS (EI, 70 eV): *m*/*z* (%) = 424 (37), 351 (32), 264 (31), 262 (20), 237 (100).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{19}N_4O_4S$ (M – H)$^-$: 423.1121; found: 423.1100.

Diethyl 1-(7-Methyl-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazol-3-yl)hydrazine-1,2-dicarboxylate (11)

Yield: 77.1 mg (88%); yellow solid; mp 193.9–195.1 °C.

IR (ATR): 3265, 2921, 1762, 1501, 1232, 1046, 809, 723 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10 (s, 1 H), 7.69 (d, *J* = 6.0 Hz, 2 H), 7.47–7.43 (m, 3 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 7.27 (d, *J* = 9.0 Hz, 1 H), 7.18 (s, 1 H), 4.59–3.95 (m, 4 H), 2.45 (s, 3 H), 1.31–1.04 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.7, 155.4, 146.4, 140.0, 135.1, 133.0, 130.5, 130.0, 129.2 , 128.1, 127.2, 126.2, 123.7, 122.2, 114.9, 64.2, 62.5, 21.3, 14.5, 14.3.

HRMS (ESI): *m*/*z* for $C_{22}H_{21}N_4O_4S$ (M – H)$^-$: 437.1278; found: 437.1295.

Diethyl 1-(6,7-Dimethyl-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazol-3-yl)hydrazine-1,2-dicarboxylate (12)

Yield: 81.4 mg (90%), yellow solid; mp 200.6–201.6 °C.

IR (ATR): 3283, 2963, 1757, 1507, 1236, 1061, 777 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.91 (s, 1 H), 7.61 (d, *J* = 7.5 Hz, 2 H), 7.35 (t, *J* = 7.5 Hz, 3 H), 7.24 (t, *J* = 7.0 Hz, 1 H), 7.18 (s, 1 H), 4.26–4.02 (m, 4 H), 2.31 (s, 3 H), 2.26 (s, 3 H), 1.20–1.05 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.6, 154.4, 145.7, 138.9, 134.1, 133.1, 132.0, 129.7, 128.3, 128.1, 127.0, 126.7 , 125.9, 125.2, 122.9, 121.0, 115.0, 63.1, 61.4, 19.3, 18.9, 13.5, 13.3.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{23}N_4O_4S$ (M – H)$^-$: 451.1434; found: 451.1429.

Diethyl 1-(2-Phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (13)

Yield: 69.9 mg (95%); yellow solid; mp 141.7–142.3 °C.

IR (ATR): 3246, 1745, 1723, 1534, 1245, 1053, 738, 685 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.71 (s, 1 H), 7.79 (d, *J* = 7.5 Hz, 2 H), 7.61 (d, *J* = 9.0 Hz, 2 H), 7.42 (t, *J* = 7.0 Hz, 2 H), 7.34 (t, *J* = 7.0 Hz, 1 H), 7.29–7.26 (m, 1 H), 6.89 (t, *J* = 6.5 Hz, 1 H), 4.36–4.06 (m, 4 H), 1.29–1.06 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.9, 155.3, 143.1, 139.5, 132.9, 128.9, 128.4, 126.9, 125.9, 124.7, 118.5, 117.4, 112.5, 64.0, 62.6, 14.4, 14.3.

LRMS (EI, 70 eV): *m*/*z* (%) = 368 (39), 295 (37), 207 (42), 181 (100), 78 (42).

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{19}N_4O_4$ (M – H)$^-$: 367.1401; found: 367.1400.

Diethyl 1-(6-Methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (14)

Yield: 67.2 mg (88%); gray solid; mp 189.7–191.1 °C.

IR (ATR): 3301, 2981, 1743, 1717, 1521, 1236, 1055, 777 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.46 (s, 1 H), 7.77 (d, *J* = 5.5 Hz, 2 H), 7.67 (s, 1 H), 7.51 (d, *J* = 8.5 Hz, 1 H), 7.39 (s, 2 H), 7.31 (s, 1 H), 7.11 (d, *J* = 7.5 Hz, 1 H), 4.39–4.20 (m, 4 H), 2.37 (s, 3 H), 1.39–1.08 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.8, 155.4, 142.1, 139.3, 133.1, 128.9, 128.2, 126.8, 122.2, 118.2, 116.7, 63.9, 62.5, 18.3, 14.4, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{21}N_4O_4$ (M – H)$^-$: 381.1559; found: 381.1566.

Diethyl 1-[2-(*p*-Tolyl)imidazo[1,2-*a*]pyridin-3-yl]hydrazine-1,2-dicarboxylate (15)

Yield: 64.9 mg (85%); yellow solid; mp 117.8–119.0 °C.

IR (ATR): 3286, 2981, 1745, 1716, 1507, 1241, 1069, 826, 755 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.69 (s, 1 H), 7.69–7.59 (m, 4 H), 7.27–7.16 (m, 3 H), 6.86 (t, *J* = 6.5 Hz, 1 H), 4.27–4.07 (m, 4 H), 2.35 (s, 3 H), 1.23–1.07 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.8, 155.3, 143.0, 139.6, 138.2, 130.0, 129.6, 126.8, 125.7, 124.6, 118.1, 117.2, 112.3, 63.9, 62.5, 62.0, 21.2, 14.4, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{21}N_4O_4$ (M – H)$^-$: 381.1559; found: 381.1567.

Diethyl 1-[2-(4-Methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl]hydrazine-1,2-dicarboxylate (16)

Yield: 72.4 mg (91%); yellow oil.

IR (ATR): 3258, 1733, 1540, 1257, 1053, 760 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.61 (s, 1 H), 7.63 (s, 1 H), 7.53 (d, *J* = 9.0 Hz, 1 H), 7.32 (s, 1 H), 7.21–7.16 (m, 3 H), 6.81–6.79 (m, 2 H), 4.15–4.06 (m, 4 H), 3.73 (s, 3 H), 1.18–0.98 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.1, 156.9, 155.2, 143.0, 139.3, 134.2, 129.9, 125.9, 119.0, 117.3, 114.6, 112.5, 112.2, 77.3, 77.1, 76.8, 64.0, 62.5, 55.3, 14.3, 14.2.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{21}N_4O_5$ (M – H)$^-$: 397.1506; found: 397.1516.

Diethyl 1-(6-Fluoro-2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (17)

Yield: 56.4 mg (73%); white solid: mp 183.5–184.3 °C.

IR (ATR): 3312, 3001, 1749, 1504, 1318, 1239, 1056, 778 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.73 (s, 1 H), 7.77–7.70 (m, 3 H), 7.58 (dd, *J* = 9.0, 4.5 Hz, 1 H), 7.40 (t, *J* = 7.5 Hz, 2 H), 7.33 (t, *J* = 7.0 Hz, 1 H), 7.18 (t, *J* = 8.0 Hz, 1 H), 4.27–4.11 (m, 4 H), 1.26–1.08 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.0, 155.0, 153.3 (d, $J_{C,F}$ = 236.3 Hz), 140.7, 140.9, 132.6, 128.9, 128.5, 126.8, 119.7, 117.8 (d, $J_{C,F}$ = 25.0 Hz), 111.7 (d, $J_{C,F}$ = 40.0 Hz), 64.1, 62.7, 62.1, 14.4, 14.3.

LRMS (EI, 70 eV): *m*/*z* (%) = 386 (25), 253 (40), 224 (52), 199 (100), 96 (36).

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{18}FN_4O_4$ (M – H)$^-$: 385.1306; found: 385.1309.

Diethyl 1-(8-Chloro-2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (18)

Yield: 69.7 mg (83%); white solid; mp 180.3–181.6 °C.

IR (ATR): 3027, 2969, 1749, 1536, 1230, 1061, 735 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.67 (s, 1 H), 7.80 (d, *J* = 7.5 Hz, 2 H), 7.45–7.32 (m, 5 H), 6.82 (t, *J* = 6.5 Hz, 1 H), 4.22–4.17 (m, 4 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.07 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.7, 155.0, 140.3, 132.5, 132.4, 128.9, 128.6, 127.1, 124.7, 123.5, 123.1, 119.8, 112.0, 64.1, 62.7, 14.3.

LRMS (EI, 70 eV): *m*/*z* (%) = 402 (27), 269 (88), 242 (56), 240 (73), 215 (100).

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{18}ClN_4O_4$ (M – H)$^-$: 401.1011; found: 401.1035.

Diethyl 1-(8-Bromo-2-phenylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (19)

Yield: 71.4 mg (80%); white solid; mp 177.4–178.7 °C.

IR (ATR): 3233, 2981, 1749, 1520, 1252, 1063, 728 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.71 (s, 1 H), 7.79 (d, *J* = 7.0 Hz, 2 H), 7.66–7.43 (m, 2 H), 7.42–7.27 (m, 3 H), 6.76 (t, *J* = 6.5 Hz, 1 H), 4.34–4.04 (m, 4 H), 1.35–1.03 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.8, 155.0, 140.8, 140.4, 132.4, 128.8 128.9, 128.2, 124.1, 119.8, 112.5, 111.5, 64.1, 62.7, 14.4, 14.3.

LRMS (EI, 70 eV): *m*/*z* (%) = 446 (31), 286 (41), 261 (92), 259 (100), 156 (39).

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{18}BrN_4O_4$ (M – H)$^-$: 445.0506; found: 445.0509.

Diethyl 1-[8-(Ethoxycarbonyl)-2-phenylimidazo[1,2-*a*]pyridin-3-yl]hydrazine-1,2-dicarboxylate (20)

Yield: 49.3 mg (56%); white solid; mp 179–181 °C.

IR (ATR): 2974, 1706, 1566, 1295, 1195, 1069, 864, 743, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.86 (s, 1 H), 8.01 (d, *J* = 7.0 Hz, 1 H), 7.82–7.80 (m, 3 H), 7.36 (t, *J* = 7.4 Hz, 2 H), 7.31–7.25 (m, 1 H), 6.92 (t, *J* = 7.0 Hz, 1 H), 4.57–4.54 (m, 2 H), 4.25–4.14 (m, 4 H), 1.51 (t, *J* = 7.0 Hz, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 0.99 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.5, 156.9, 155.0, 140.5, 140.2, 132.3, 130.1, 128.7, 128.6, 126.9, 119.8, 118.9, 111.4, 64.0, 62.6, 61.6, 14.4, 14.2.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{25}N_4O_6$ (M + H)$^+$: 441.1769; found: 441.1783.

Diethyl 1-[2-(4-Bromophenyl)imidazo[1,2-*a*]pyridin-3-yl]hydrazine-1,2-dicarboxylate (21)

Yield: 58.9 mg (66%); yellow solid; mp 189.6–191.3 °C.

IR (ATR): 3243, 2986, 1749, 1530, 1242, 1061, 837, 756, 668 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.70 (s, 1 H), 7.90 (s, 1 H), 7.76–7.54 (m, 3 H), 7.50 (d, *J* = 6.5 Hz, 2 H), 7.28 (s, 1 H), 6.90 (s, 1 H), 4.35–4.19 (m, 4 H), 1.30–1.13 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.7, 155.1, 143.1, 138.4, 132.0, 131.8, 128.5, 126.1, 124.7, 122.5, 118.6, 117.3, 112.7, 64.1, 62.6, 14.4, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{18}BrN_4O_4$ (M – H)$^-$: 445.0506; found: 445.0518.

Diethyl 1-[2-([1,1′-Biphenyl]-4-yl)imidazo[1,2-*a*]pyridin-3-yl]hydrazine-1,2-dicarboxylate (22)

Yield: 71.0 mg (80%); yellow solid: mp 192.5–193.4 °C.

IR (ATR): 3106, 2914, 1739, 1537, 1245, 1056, 740 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.71 (s, 1 H), 7.88 (d, *J* = 8.0 Hz, 2 H), 7.64 (dd, *J* = 17.5, 8.0 Hz, 6 H), 7.45 (t, *J* = 7.5 Hz, 2 H), 7.36 (t, *J* = 7.5 Hz, 1 H), 7.29 – 7.26 (m, 1 H), 6.89 (t, *J* = 6.5 Hz, 1 H), 4.27–4.11 (m, 4 H), 1.25–1.05 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.9, 155.3, 143.2, 141.0, 140.5, 139.1, 131.8, 128.8, 127.6, 127.5, 127.3, 127.0, 125.9, 124.7, 118.5, 117.4, 112.5, 64.0, 62.6, 14.4, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{23}N_4O_4$ (M – H)$^-$: 443.1714; found: 443.1729.

Diethyl 1-(2-(Naphthalen-2-yl)imidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (23)

Yield: 70.2 mg (84%); yellow solid; mp 71.2–72.5 °C.

IR (ATR): 3231, 2916, 1731, 1503, 1236, 1058, 755 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.73 (s, 1 H), 8.31 (s, 1 H), 7.88–7.82 (m, 5 H), 7.64 (d, *J* = 8.5 Hz, 1 H), 7.48 (d, *J* = 2.9 Hz, 2 H), 7.27 (s, 1 H), 6.88 (s, 1 H), 4.29–4.08 (m, 4 H), 1.28–1.03 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.9, 155.3, 143.2, 133.54, 133.1, 130.2, 128.5, 128.4, 127.6, 126.4, 126.3, 125.9, 124.6, 124.4, 118.8, 117.3, 112.5, 64.0, 62.5, 62.1, 14.3, 14.2.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{21}N_4O_4$ (M – H)$^-$: 417.1557; found: 417.1573.

Diethyl 1-(2-Methylimidazo[1,2-*a*]pyridin-3-yl)hydrazine-1,2-dicarboxylate (24)

Yield: 33.0 mg (54%); yellow oil.

IR (ATR): 3244, 2979, 1733, 1537, 1229, 1066, 760 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.40 (s, 1 H), 7.64 (s, 1 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.14 (s, 1 H), 6.76 (s, 1 H), 4.26–4.09 (m, 4 H), 2.31 (s, 3 H), 1.23–1.15 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.8, 138.1, 127.7, 125.4, 124.1, 123.0, 118.3, 115.8, 111.1, 62.8, 61.5, 13.4, 11.9.

LRMS (EI, 70 eV): *m*/*z* (%) = 306 (48), 218 (49), 144 (46), 119 (100), 78 (51).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{17}N_4O_4$ (M – H)$^-$: 305.1244; found: 305.1244.

Diethyl 1-(2-Phenylimidazo[1,2-*a*]pyrimidin-3-yl)hydrazine-1,2-dicarboxylate (25)

Yield: 56.8 mg (77%); yellow solid; mp 142.9–144.0 °C.

IR (ATR): 3223, 1748, 1506, 1458, 1233, 1056, 756 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.06 (s, 1 H), 8.58 (s, 1 H), 7.89 (d, *J* = 7.0 Hz, 2 H), 7.82 (s, 1 H), 7.41 (d, *J* = 6.0 Hz, 2 H), 7.35 (d, *J* = 6.0 Hz, 1 H), 6.94 (s, 1 H), 4.19 (d, *J* = 7.5 Hz, 4 H), 1.28–1.03 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.1, 154.9, 151.0, 145.8, 141.0, 132.7, 132.2, 128.8, 127.2, 116.8, 108.8, 64.2, 62.7, 14.3.

LRMS (EI, 70 eV): *m*/*z* (%) = 369 (22), 296 (30), 209 (16), 182 (100), 79 (26).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{18}N_5O_4$ (M – H)$^-$: 368.1535; found: 368.1367.

Diisopropyl 1-(6-Phenylimidazo[2,1-*b*]thiazol-5-yl)hydrazine-1,2-dicarboxylate (26)

Yield: 57.9 mg (72%); white solid; mp 168–170 °C.

IR (ATR): 2981, 1733, 1603, 1450, 1242, 973, 784, 716 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.86–7.78 (m, 1 H), 7.73–7.63 (m, 2 H), 7.41–7.34 (m, 2 H), 7.29–7.25 (m, 1 H), 7.11 (s, 1 H), 6.82–6.73 (m, 1 H), 5.06–4.93 (m, 2 H), 1.35–1.00 (m, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.5, 154.6, 148.1, 140.9, 133.2, 128.8, 127.8, 126.3, 120.4, 119.4, 112.0, 72.2, 70.6, 21.9.

LRMS (EI, 70 eV): *m*/*z* (%) = 401 (65), 314 (100), 187 (48), 229 (48), 273 (46).

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{23}N_4O_4S$ (M + H)$^+$: 403.1435; found: 403.1451.

Imidazoheterocycle-Carbamates; Ethyl (6-Phenylimidazo[2,1-*b*]thiazol-5-yl)carbamate (27); Typical Procedure

A 15 mL tube with a Teflon cap, equipped with a magnetic stirring bar, was charged with substrate **3** (75 mg, 0.20 mmol) and Cs_2CO_3 (130 mg, 0.40 mmol, 2 equiv) in MeCN (2 mL). To this mixture was added ethyl bromoacetate (33 mg, 0.20 mmol, 1 equiv), and the mixture was heated at 80 °C until the starting material was consumed, as indicated by TLC. The mixture was quenched with sat. aq NH_4Cl and extracted with EtOAc. The extracts were collected and washed with brine, dried (anhyd Na_2SO_4) and concentrated in vacuo. The resulting residue was purified by column chromatography to give product **27**; yield: 45.3 mg (79%), yellow solid; mp 145.7–146.6 °C.

IR (ATR): 2978, 1564, 1461, 1239, 1093, 979, 860 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.79–7.64 (m, 3 H), 7.18–7.01 (m, 4 H), 6.59 (s, 1 H), 4.12 (s, 2 H), 1.20 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.2, 146.9, 139.6, 133.2, 128.4, 128.3, 127.3, 126.4, 116.3, 112.4, 62.2, 14.5.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{14}N_3O_2S$ (M + H)$^+$: 288.0801; found: 288.0807.

Ethyl [6-(4-Methoxyphenyl)imidazo[2,1-*b*]thiazol-5-yl]carbamate (28)

Yield: 45.6 mg (72%); white solid; mp 114.3–115.6 °C.

IR (ATR): 2971, 1703, 1539, 1452, 1256, 958, 887 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.66 (s, 2 H), 7.12 (s, 1 H), 6.81–6.68 (s, 3 H), 4.22 (s, 2 H), 3.77 (s, 3 H), 1.30–1.12 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.9, 155.3, 146.7, 139.7, 127.7, 126.0, 117.3, 115.4, 113.8, 112.0, 77.4, 77.1, 76.9, 62.2, 55.2, 14.5.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{16}N_3O_3S$ (M + H)$^+$: 318.0907; found: 318.0912.

Ethyl [6-(4-Chlorophenyl)imidazo[2,1-*b*]thiazol-5-yl]carbamate (29)

Yield: 39.2 mg (61%); yellow solid; mp 179.8–180.5 °C.

IR (ATR): 2974, 1626, 1470, 1242, 965, 851 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.69 (s, 1 H), 7.31–7.23 (m, 2 H), 7.23 (s, 1 H), 6.99 (s, 1 H), 6.81 (s, 1 H), 4.24 (s, 2 H), 1.26 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.9, 147.2, 138.9, 133.2, 131.8, 128.7, 127.6, 117.2, 116.0, 112.8, 62.5, 14.5.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{13}ClN_3O_2S$ (M + H)$^+$: 322.0412; found: 322.0417.

Ethyl (2-Phenylbenzo[*d*]imidazo[2,1-*b*]thiazol-3-yl)carbamate (30)

Yield: 59.9 mg (89%); yellow solid; mp 151.6–152.8 °C.

IR (ATR): 2973, 1533, 1414, 1382, 1245, 1053, 885, 738 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.81 (s, 2 H), 7.67 (s, 2 H), 7.39 (m, 4 H), 7.26 (s, 1 H), 4.34–4.09 (m, 2 H), 1.40–1.24 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.5, 145.7, 132.9, 132.4, 130.2, 129.1, 128.4, 127.5, 126.4, 126.1, 124.7, 124.0, 117.8, 112.9, 62.5, 14.6.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{16}N_3O_2S$ (M + H)$^+$: 338.0958; found: 338.0962.

Ethyl [2-(4-Chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]carbamate (31)

Yield: 48.7 mg (77%); yellow solid; mp 165.7–166.5 °C.

IR (ATR): 2973, 1633, 1513, 1334, 1235, 1053, 838, 758 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.85 (s, 1 H), 7.74–7.65 (m, 3 H), 7.49 (d, *J* = 7.5 Hz, 1 H), 7.16 (d, *J* = 6.5 Hz, 3 H), 6.77 (t, *J* = 6.0 Hz, 1 H), 4.23 (s, 2 H), 1.43–1.10 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.2, 142.6, 138.0, 133.7, 131.3, 128.5, 128.2, 125.4, 122.5, 117.3, 114.5, 112.6, 62.3, 14.5.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{15}ClN_3O_2$ $(M + H)^+$: 316.0847; found: 316.0848.

Ethyl (2-Phenylimidazo[1,2-*a*]pyrimidin-3-yl)carbamate (32)

Yield: 23.1 mg (41%); yellow solid; mp 157.3–158.5 °C.

IR (ATR): 2983, 1718, 1556, 1453, 1239, 956, 869, 766 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.43 (s, 1 H), 8.18 (s, 1 H), 7.92 (s, 2 H), 7.35–7.30 (m, 3 H), 6.82 (s, 1 H), 4.25 (s, 2 H), 1.33–1.26 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.9, 150.4, 145.3, 140.0, 132.0, 128.6, 128.5, 127.5, 113.0, 108.7, 62.5, 14.5.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{15}N_4O_2$ $(M + H)^+$: 283.1190; found: 283.1199.

Cinnoline Derivatives; Pyrido[2′,1′:2,3]imidazo[4,5-*c*]cinnoline (33); Typical Procedure

To a stirred mixture of **13** (74 mg, 0.20 mmol) in trifluoroacetic acid (1 mL) was added $PhI(OAc)_2$ (161 mg, 0.5 mmol, 2.5 equiv) at r.t. The reaction was brought to r.t. and then stirred for 12 h. The progress of the reaction was monitored by TLC. After completion, the reaction was quenched with ice cooled water, neutralized with sat. aq $NaHCO_3$, and then extracted with EtOAc. The organic layers were combined, washed with brine, dried (anhyd Na_2SO_4), and concentrated in vacuo. The resulting residue was purified by column chromatography to give the product **33**; yield: 35.6 mg (81%); white solid; mp 202.2–203.1 °C.

IR (ATR): 2928, 1617, 1523, 1234, 1245, 1053, 752 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.33 (d, *J* = 6.5 Hz, 1 H), 8.74–8.70 (m, 2 H), 7.93–7.92 (m, 3 H), 7.80–7.77 (m, 1 H), 7.24 (t, *J* = 7.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.4, 148.6, 141.8, 134.2, 133.2, 130.6, 130.2, 129.3, 125.2, 122.0, 120.1, 118.0, 113.2.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_9N_4$ $(M + H)^+$: 221.0822; found: 221.0830.

9-Methylthiazolo[2′,3′:2,3]imidazo[4,5-*c*]cinnoline (34)

Yield: 32.6 mg (68%); white solid; mp 206.6–207.4 °C.

IR (ATR): 2921, 1613, 1508, 1257, 993, 845, 761 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.65 (d, *J* = 7.5 Hz, 1 H), 8.55 (d, *J* = 7.5 Hz, 1 H), 8.06 (s, 1 H), 7.85 (s, 2 H), 2.61 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.4, 147.9, 142.8, 136.3, 130.6, 129.9, 128.5, 128.0, 121.4, 120.2, 114.4, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_9N_4S$ $(M + H)^+$: 241.0543; found: 241.0540.

Benzo[4′,5′]thiazolo[2′,3′:2,3]imidazo[4,5-*c*]cinnoline (35)

Yield: 29.8 mg (54%); white solid; mp 203.5–204.6 °C.

IR (ATR): 2978, 1625, 1534, 1238, 1061, 905, 746 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.81 (d, *J* = 8.0 Hz, 1 H), 6.67–6.66 (m, 1 H), 8.55–8.53 (m, 1 H), 7.89–7.83 (m, 2 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.67 (t, *J* = 7.5 Hz, 1 H), 7.47 (t, *J* = 7.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.5, 148.0, 144.5, 137.0, 131.9, 130.9, 130.0, 128.8, 127.7, 125.9, 124.0, 121.4, 120.0, 115.5.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_9N_4S$ $(M + H)^+$: 277.0543; found: 252.0547.

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Supporting Information

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