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Dienophilicity of imidazole in inverse electron demand Diels–Alder reactions: cycloadditions with 1,2,4,5-tetrazines and the structure of zarzissine

Zhao-Kui Wan, Grace H. C. Woo and John K. Snyder*

Department of Chemistry, Boston University, 590 Commonwealth Avenue, Boston, MA 02215, USA

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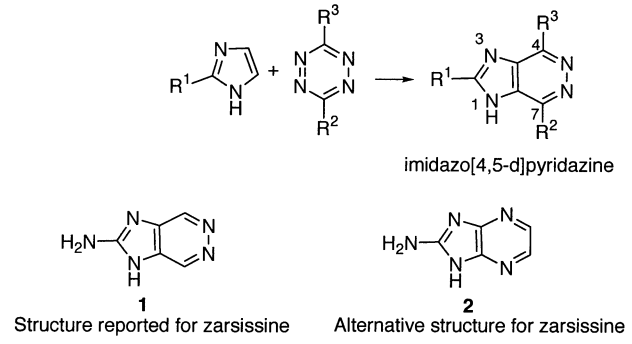
Abstract—The inverse electron demand cycloadditions of 2-substituted imidazoles with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate produced imidazo[4,5-*d*]pyridazines in good yields. This chemistry was applied to the synthesis of 2-amino-1*H*-imidazo[4,5-*d*]pyridazine (**1**), the structure reported for zarzissine, a cytotoxic marine alkaloid. Differences in the ^{1}H- and ^{13}C NMR spectra of **1** with those reported for zarzissine necessitated a structural revision, and zarzissine was then considered to be the corresponding 2-amino-1*H*-imidazo[4,5-*b*]pyrazine (**2**), which was subsequently synthesized from the parent heterocycle.

1. Introduction

Imidazole is a fundamental structural unit of numerous biologically active natural products,[1] and its chemistry[2] has been investigated extensively. Research into imidazole chemistry has been quite comprehensive; single site functionalizations and substitutions, as well as various annulation strategies[3] have been well documented. We have been interested in the dienophilicity of heteroaromatic compounds with latent enamine functionalities in inverse electron demand Diels–Alder reactions, and the development of this chemistry for synthesis, primarily concentrating on indole,[4] and to a lesser extent pyrrole[5] and imidazole. The dienophilic potential of imidazole has been largely neglected except for two reports by Seitz[6] using imidazole derivatives as dienophiles in reactions with 1,2,4,5-tetrazines, and demonstrations by Horne of the cycloaddition pathway of 2-aminoimidazole with its in situ generated Schiff bases in condensation reactions with aldehydes.[7] In addition, our preliminary investigations into the reactions of imidazoles with 1,2,4-triazines in both inter-[8] and intramolecular[9] cycloadditions leading to the preparation of 3-deazapurines, 8-deazapteridines, and 1,5-naphthyridines have been communicated.

We have undertaken further investigations into the reactions between imidazoles and 1,2,4,5-tetrazines as a method for preparing imidazo[4,5-*d*]pyridazines as purine analogues (Scheme 1). The recent report by Dang on the cycloaddition between 4-aminoimidazoles and triethyl 1,3,5-triazine-2,4,6-tricarboxylate leading the corresponding purines testifies to the interest in this area in the search for new drug candidates.[10] The cytotoxic marine natural product zarzissine, deduced to be 2-amino-1*H*-imidazo[4,5-*d*]pyridazine (**1**),[11] became our initial target. Zarzissine was reported to have a broad range of activities, being active against *S. aureus*, the fungi *Candida albicans* and *C. tropicais*, as well as against several tumor cell lines. Given its simple structure, a straightforward synthetic approach such as a cycloaddition strategy readily amenable to analogue preparation became our objective.



Scheme 1.

Other imidazo[4,5-*d*]pyridazines have been the focus of chemical and biological investigations,[12] but previous routes to this heterocyclic system can be rather tedious. For example, the construction of the imidazo[4,5-*d*]pyridazine system usually requires a 4,5-dicarbonylated imidazole[13] or 4,5-diaminopyridazine[14] as starting material

Keywords: imidazole; inverse electron demand Diels–Alder cycloadditions; zarzissine; imidazo[4,5-*d*]pyridazines; imidazo[4,5-*d*]pyrazine.

* Corresponding author. Tel.: +617-353-2621; fax: +617-353-6466; e-mail: jsnyder@chem.bu.edu

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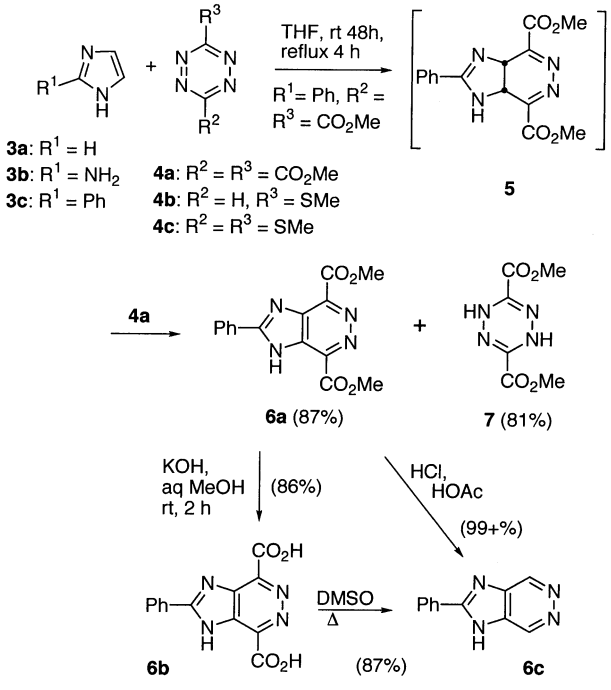
which require several steps to prepare. Seitz had shown that imidazoles will undergo cycloadditions with 1,2,4,5-tetrazines to produce these condensed pyridazine systems, but imidazole ring-opened products often dominated the product mixture.[6b] We now report results examining the scope of the dienophilicity of imidazoles with 1,2,4,5-tetrazines, and the synthesis of **1**, whose NMR data differed significantly from that reported for zarzissine. Zarzissine was then considered to be the corresponding 2-amino-1*H*-imidazo[4,5-*b*]pyrazine (**2**), which was also synthesized. While the ^{1}H NMR data for **2** in the protonated state were quite similar to those reported for zarzissine, there were some differences in the ^{13}C NMR chemical shifts as well as in the UV spectra.

2. Results and discussion

2.1. Synthesis of imidazo[4,5-*d*]pyridazines

Initial experiments examining the cycloadditions of imidazole (**3a**) and 2-aminoimidazole (**3b**) with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**4a**)[15] were fruitless, yielding only intractable mixtures of unstable compounds. Attempted reactions of **3a** and **3b** with mono- and bis-methylthiotetrazines **4b**[16] and **4c**,[17] respectively, were also unproductive, giving an intractable mixture of products. The parent, unsubstituted 1,2,4,5-tetrazine, the cycloaddition of which with **3b** would provide a direct route to **1**, is a highly volatile compound which was prepared[18] in low overall yield due to difficulty in handling, so this was not further pursued.[19] Since Seitz had been successful in reacting 2-methylimidazole with 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine,[6b] we turned to other 2-substituted imidazoles which might be better behaved in reactions with **4a**. 2-Phenylimidazole (**3c**) reacted cleanly with tetrazine **4a** (2 equiv.) in THF to give aromatized cycloadduct **6a** (87%), along with 1,4-dihydrotetrazine **7**[4a] (81%, Scheme 2). Presumably **7** arises from the dehydrogenation of the initially formed dihydroadduct **5** by the extra equivalent of **4a**, as also found in the cycloadditions of indole with **4a**.[4a,20] Hydrolysis of **6a** (KOH, 3 equiv. in 1/1 aq MeOH) gave unstable dicarboxylic acid **6b** (86% crude yield), which was immediately decarboxylated (refluxing DMSO/H_2O, 1/1, v/v) to 2-phenyl-1*H*-imidazo[4,5-*d*]pyridazine **6c** (75% from **6a**).[21] Alternatively, direct demethoxycarbonylation of **6a** in refluxing HCl/HOAc (1/1, v/v)[22] gave **6c** in quantitative yield.[23]

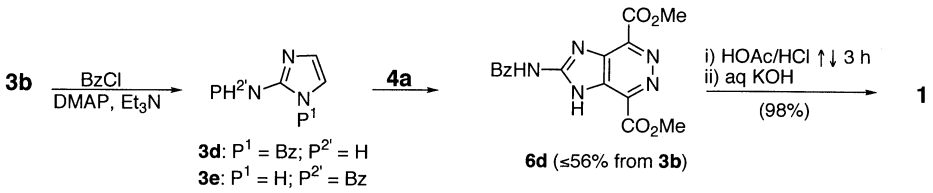


Scheme 2.

With the feasibility of the inverse electron demand cycloaddition of **3c** established as a route to 2-substituted imidazo[4,5-*d*]pyridazines, the purported zarzissine skeleton, protection of **3b** was examined as a means to coax productive dienophilicity from its chemistry with **4a**. Benzoylation of **3b** following neutralization[24] of its commercially available sulfate salt gave a mixture of mono and dibenzoylated products including the N^1 and $N^{2'}$ monoprotected **3d** and **3e**, respectively, whose ratio varied considerably from batch-to-batch (Scheme 3). Purification of **3d** and **3e** by silica gel chromatography proved impossible due to instability, but reaction of a crude mixture of **3d** and **3e** with tetrazine **4a** (2 equiv., THF, rt) gave the desired zarzissine precursor **6d**, the yield of which varied with the amount of **3e** in the benzoylation product mixture (30–56% from **3b**).

The conclusion was therefore reached that N^1-benzoylated **3d** did not undergo a cycloaddition with **4a**, and that cycloadduct **6d** resulted solely from the reaction of **3e**. Acyl migration from N^1 to $N^{2'}$, which has been observed previously in 1-acylated 2-aminobenzimidazoles,[25] was ruled out by control experiments. N^1-Benzoyl-2-aminoimidazole (**3d**) was ultimately obtained without any **3e** by variation of the benzoylation conditions, and indeed, **3d** failed to yield a cycloadduct with **4a**. Furthermore, resubjecting **3d** to the benzoylation conditions without the benzoyl chloride did not produce any **3e**. It was therefore concluded that N^1-acylated imidazoles were significantly poorer dienophiles than the N^1-unsubstituted compounds. Seitz has reported the successful cycloaddition of N-methylimidazole with both **4a**[6a] and 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine,[6b] so N-1 substitution alone is not responsible for the lowered dienophilicity, which presumably is also a consequence of the lowered LUMO of **3d**. This low reactivity of **3d** contrasts with the excellent dienophilicity of the corresponding N-benzoylindole in cycloadditions with **4a**.[4a]

Interestingly, the ^{1}H NMR spectrum of **6d** ($CDCl_3$, rt) showed two distinct, broad singlets for the methoxyl resonances (δ 4.19 and 3.90, both s, 3H) indicative of relatively slow equilibration of the imidazole proton between the N1 and N3 positions, presumably due to intramolecular hydrogen bonding with the amide carbonyl. Coalescence of these resonances occurred at 50°C (δ 4.05). In contrast, the methoxyl resonances of **6a** appeared as one sharp singlet (δ 4.10, s, 6H) indicative of more rapid equilibration. Cycloadduct **6d** was demethoxycarbonylated and debenzoylated in one pot by refluxing in HCl/HOAc (1/1, v/v, 3 h), followed by removal of the solvent in vacuo and



Scheme 3.

basic work-up to give the desired **1** in a maximum 55% overall yield from **3b**.

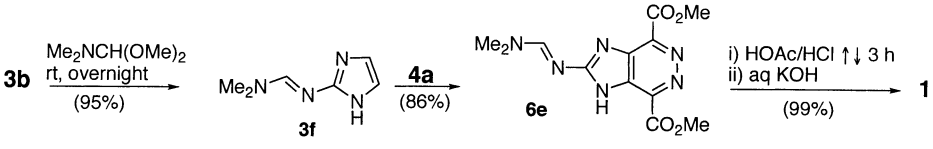
The difficulty in preparing **3e** in reproducible yield, however, stimulated a search for another $N^{2'}$-protecting group for 2-aminoimidazole. Taylor has successfully employed *N*,*N*-dimethylaminoimine protection of primary amines in his pteridine and folate studies,[26] prepared from *N*,*N*-dimethylformamide dimethyl acetal.[27] Adapting this strategy to 2-aminoimidazole, protection of **3b** gave dimethylaminoimine **3f** in 95% yield (Scheme 4). The cycloaddition between **3f** and **4a** proceeded smoothly (even at −78°C!) to give **6e** (86%). Simultaneous demethoxycarbonylation and deprotection in refluxing HCl/HOAc gave a quantitative yield of **1**, in a highly reproducible 75% overall yield from **3b**.

The ^{1}H- and ^{13}C NMR spectra of synthetic **1**, however, were not in agreement with the data reported for natural zarzissine, though the UV spectral data were similar.[11] Of note, the resonance of the aromatic proton (H1/H4) of **1** (DMSO-d_6, δ 8.89, s) was significantly downfield from that reported for zarzissine (DMSO-d_6, δ 8.09, s), though this lowfield shift of synthetic **1** is typical of other imidazo[4,5-*d*]pyridazines reported in the literature.[28] The ^{13}C chemical shifts of synthetic **1** as well as its HCl salt were also significantly different from those reported for zarzissine.

Given the proton chemical shifts reported for zarzissine, a more likely structure for zarzissine was thought to be 2-amino-1*H*-imidazo[4,5-*b*]pyrazine (**2**), which is intuitively more satisfying from a biosynthetic viewpoint, conceivably arising from two glycine molecules and a guanidinium ion. A comparison of chemical shifts of related imidazo[4,5-*b*]pyrazines with the corresponding imidazo[4,5-*d*]pyridazines indicated that the resonances of the aromatic protons of the latter class of compounds appear approximately 0.8 ppm downfield from the corresponding resonances of the former.[28] The chemical shift of the sole aromatic proton reported for zarzissine therefore falls in the range of the corresponding imidazo[4,5-*b*]pyrazines, 0.8 ppm upfield from that found in **1**. We therefore set out to prepare **2** to resolve the structure of zarzissine.

2-Amino-1*H*-imidazo[4,5-*b*]pyrazines are very rare. The only synthetic procedure found in the literature employs a Hg(II) promoted condensation of phenylmethylamine with 1*H*-imidazo[4,5-*b*]pyrazin-2-ol,[29] a procedure we wished to avoid due to the use of mercury. Other efforts to prepare **2** were adapted from the numerous synthetic procedures available to prepare 2-aminobenzimidazoles[3b,30] and related systems which followed two general strategies: (1) condensations of 2,3-diaminopyrazine,[31] or (2) condensations of 2,3-dichloropyrazine.[32] These efforts, all of which failed, are summarized in Chart 1. The low reactivity of 2,3-diaminopyrazine in these condensations in comparison to *o*-phenylenediamine can be ascribed to the electron deficiency of the pyrazine ring, reducing the nucleophilicity of the amino groups. For example, the requisite intermediate thioureas were not produced in the procedures described in Items 1 and 5. Attempts to adapt Buchwald's nickel catalyzed amination[33] to 2,3-dichloropyrazine with *N*,*N*′-di-Boc-*N*″triflylguanidinium[31e] (Item 10) were also unsuccessful.

While these attempts were not fruitful, the parent heterocycle imidazo[4,5-*b*]pyrazine (**8**) was prepared from commercially available 2,3-dichloropyrazine following literature procedures[32] (Scheme 5). Protection of **8** with either MOMCl or BOMCl followed by imidazole deprotonation[34] and subsequent addition of tosylazide following Evans' examples for enolate azidation[35] gave **10a** and **10b** in good yields.[36] In both cases, the desired azides were accompanied by considerable amounts of dimer **11a** and **11b**,[37] respectively, with the BOM protection being the most effective in our hands. The amount of dimer could be minimized by performing the reaction in toluene rather than THF, and using a lithium base for the deprotonation. Thus, in THF with KHMDS, dimer **11a** was the sole product from the reaction of **9a**, isolated in 71% unoptimized yield. When a freshly generated solution of LDA in THF was added to a solution of **9a** or **9b** in toluene, only 16% and 11% yields of **11a** and **11b**, respectively, were obtained with the dominant products being the desired azidoimidazopyrazines **10a** (57%) and **10b** (69%), respectively. Trisyl azide (2,4,6-triisopropylbenzenesulfonyl azide) failed as the azide transfer reagent, and the use of the PNB or triphenylmethyl (trityl) protecting groups (**9c** and **9d**, respectively) also failed to give the desired azide, resulting only in recovered imidazopyrazine after work-up.



Scheme 4.

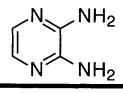
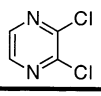
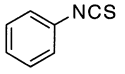
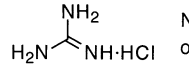
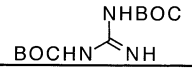
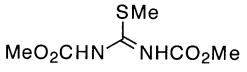
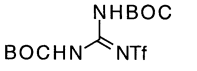
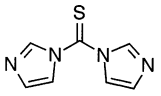
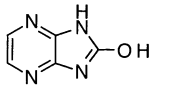
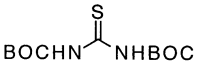
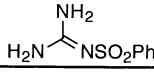
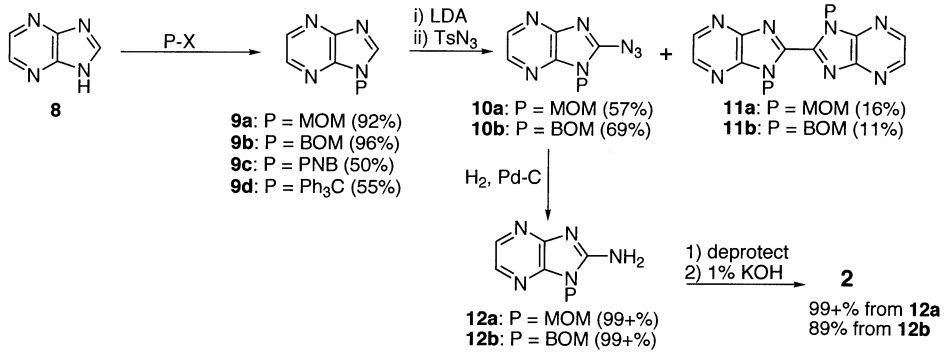
Item	Condensations with 	ref.[a]	Item	Condensations with 	ref.[a]
1	 $PhNH_2$, Et_3N, MeCN then HgO, S_8, EtOH	3b,31a	9	 NaH, DMF or Cu, H_2O, 140 °C	32
2	NH_2CN	31b	10	 $Ni(COD)_2$, DPPF tert-BuOK, tol	33
3	 $HgCl_2$, Et_3N, DMF or HOAc, MeOH	31c,d			
4	 Et_3N, DMF	31e		**Other Procedure**	
5	 $BnNH_2$, MeCN or HgO, S_8, EtOH	31f	11	 $PhOP(O)(NH_2)_2$ or $POCl_3$, then NH_3	31k-o
6	BrCN	31g-h			
7	 Mukaiyama reagent Et_3N, DMF or THF	31i			
8	 200 - 230 °C (fusion)	31j			

Chart 1. Failed condensation reactions attempted to prepare **2**. [a] References give citations from which procedures were adapted.

Reduction (H_2/Pd-C) of **10a** and **10b** to the amines **12a** and **12b**, respectively, and deprotection followed by basic work-up gave the target **2** as the free base.

Comparison of the NMR and UV data of **2** and its HCl salt with that reported for zarzissine revealed that the chemical shift of the sole nonexchangeable proton of the HCl salt matched that reported for zarzissine, but the ^{13}C chemical shifts of the same sample, which had to be recorded at 50°C due to severe line broadening, and UV absorptions showed distinct differences (Table 1). An investigation of the sensitivity of the ^{1}H chemical shifts of **1** and **2** and their HCl salts to concentration showed little variation ($\Delta\delta \leq 0.1$ ppm) from 0.0005–0.1 M. Varying amounts of water (H_2O) in the DMSO-d_6 also did not affect the chemical shifts.

Horne has reported large ^{13}C chemical shift differences between neutral and protonated glycocyamidine derivatives (2-aminoimidazolines) with the guanidine carbons undergoing 12–17 ppm upfield shifts upon protonation.[38] Furthermore, the exact chemical shifts of the protonated compounds proved to be very sensitive to the degree of



Scheme 5.

Table 1. Comparison of spectroscopic data for **1** and **2** with that reported for zarzissine

	1	**1**·HCl	**2**	**2**·HCl	Zarzissine[a]
UV (MeOH) $_{\lambda\,max}$ (log ϵ)	206 (4.22), 230 (sh), 262 (3.71), 308 (sh)	206 (4.26), 225 (sh), 262 (3.76), 306 (2.84)	217 (sh), 244 (3.30), 318 (4.03)	217 (sh), 244 (3.62), 318 (4.39)	206 (4.61), 259 (3.91)
^{1}H NMR[b]	11.5 (bs, NH), 8.94 (bs, 2H), 6.97 (bs, NH_2)	9.26 (bs, 2H), 8.20 (bs, NH_3)	11.74 (bs, NH), 7.78 (bs, 2H), 7.12 (bs, NH_2)	8.79 (bs, NH_3), 8.09 (bs, 2H)	12.80 (bs, NH), 8.09 (bs, 2H), 7.11 (bs, NH_2)
^{13}C NMR[b]	159.9, 138.8, 136.1	161.9, 140.7, 132.8	158.7, 146.9, 133.4[c]	155.0, 141.6, 131.9[c]	155.2, 152.4, 139.4

[a] As reported in Ref. 11.
[b] Recorded in DMSO-d_6.
[c] Recorded at 50°C; two upfield resonances were not observed at rt due to line broadening.

protonation, and the identity of the counter anion (chloride vs acetate, for example, resulted in the differences of >20 ppm as a consequence of the ability to form the dihydrogen chloride salts with HCl, which was not possible with acetic acid). Given the uncertainty over: (1) the exact state of protonation of the isolated zarzissine, (2) the presence of a possible counterion should the natural product have been isolated in a protonated or partially protonated state, and (3) the precise conditions under which the NMR spectra of the natural product were recorded, reproducing the spectral data becomes a near-impossible task without a sample of zarzissine in hand. Unfortunately, neither an authentic sample, nor authentic spectra of zarzissine were made available for direct comparison. We believe the most reasonable structure for zarzissine is **2**, but the true identity of zarzissine remains unconfirmed.

3. Conclusion

In summary, 2-substituted imidazoles have proven to be good dienophiles in inverse electron demand Diels–Alder reactions with 1,2,4,5-tetrazine **4a** producing imidazo[4,5-*d*]pyridazines in excellent yields. Applying this chemistry, the structure reported for the marine cytotoxic agent zarzissine, 2-amino-1*H*-imidazo[4,5-*d*]pyridazine (**1**), was synthesized, which proved to have spectroscopic data quite different from that reported for zarzissine. It was then considered that the biosynthetically more appealing 2-amino-1*H*-imidazo[4,5-*b*]pyrazine (**2**) might be the correct structure for zarzissine, and after considerable effort, this compound was also synthesized. While the proton data reported for zarzissine approximated that of protonated **2**, differences existed in the ^{13}C chemical shifts and UV spectra. Nevertheless, imidazo[4,5-*d*]pyridazines are of general interest as purine analogues [12a,12b,12c,13,14,39] due to a variety of biological activities including angiotensin II antagonism[40] and cardiotonic activity.[28,41] This inverse electron demand cycloaddition chemistry of imidazole with 1,2,4,5-tetrazine **4a** represents a quick and easy route to this heterocyclic system.

4. Experimental

4.1. General methods

Melting points were determined in capillaries and are uncorrected; ^1H- and ^{13}C NMR spectra were recorded at 93.94 kG (^1H 400 MHz, ^{13}C 100 MHz) 70.5 kG (^1H 300 MHz, ^{13}C 75 MHz) and 63.41 kG (^1H 270 MHz, ^{13}C 67.5 MHz) in $CDCl_3$, DMSO-d_6, CD_3OD, and acetone-d_6 (0.5 mL) as indicated. The δ 7.24 resonance of residual $CHCl_3$, δ 2.49 protio resonance of residual DMSO-d_5, δ 3.31 protio resonance of residual CHD_2OD, and the δ 2.05 protio resonance of residual acetone-d_5 were used as internal references for the ^1H spectra recorded in these solvents, respectively. The center line of the $^{13}CDCl_3$ triplet (δ 77.0), the center line of the $CD_3S(O)^{13}CD_3$ septet (δ 39.5), the center line of the $^{13}CD_3OD$ septet (δ 49.2), and the center line of the $CD_3C(O)^{13}CD_3$ septet (δ 29.9) were used as internal references for the ^{13}C spectra, respectively. All exchangeable proton resonances (NH) in non-exchanging solvents were identified by the addition of D_2O. Infrared spectra were recorded on NaCl plates or as KBr pellets. Solid samples were deposited on the NaCl plate as a solution in an appropriate, volatile solvent (typically CH_2Cl_2) followed by evaporation of the solvent. Only diagnostic bands, such as NH, imine, and carbonyl stretching bands, are reported.

Imidazole (**3a**, Aldrich), 2-aminoimidazole sulfate salt (**3b**, Aldrich), 2-phenylimdazole (**3c**, Aldrich), and 1,2-dichloropyrazine (Pfaltz and Bauer) were were commercially available and used without further purification. Tetrazines **4a**,[15] **4b**,[16] and **4c**[17] were prepared according to literature procedures. All organic solvents were dried and distilled according to standard procedures[42] immediately before use. Flash chromatography was performed using flash silica gel (43–60 μm).[43]

4.1.1. Dimethyl 2-phenyl-1*H*-imidazo[4,5-*d*]pyridazine-4,7-dicarboxylate (6a). A solution of 2-phenylimidazole (**3c**, 74.3 mg, 0.5 mmol) and dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**4a**, 198 mg, 1.0 mmol) in anhydrous THF (8 mL) under argon was stirred at rt for 48 h, then refluxed 4 h. The resultant orange solution was evaporated in vacuo and the residue purified by flash chromatography (EtOAc/hexanes, 1:1 to elute **7**, then 2:1 to elute **6a**) to give **6a** (140 mg, 87%) as yellow solid. Mp 142–145°C; IR (NaCl) 3400–3040, 1734 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 12.5 (bs, NH), 8.45 (dd, J=8.1, 1.7 Hz, 2H), 7.68–7.60 (m, 3H), 4.10 (s, 6H); ($CDCl_3$, 400 MHz) δ 10.95 (bs, NH), 8.24 (dd, J=8.0, 1.2 Hz, 2H), 7.63–7.56 (m, 3H), 4.18 (s, 6H); ^{13}C NMR (acetone-d_6, 67.5 MHz) δ 164.8, 159.7, 143.2, 139.6, 132.9, 129.7, 129.6, 128.9, 53.4; (in $CDCl_3$, 67.5 MHz, not all peaks were resolved); CIHRMS (NH_3, 140 eV) m/z 313.0936 ($[M+1]^+$, calcd for $C_{15}H_{12}N_4O_4$, 313.0936); Dimethyl 1,3-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate **7**[4a] was also isolated (81.3 mg, 81.3%).

4.1.2. 2-Phenyl-1*H*-imidazo[4,5-*d*]pyridazine-4,7-dicarboxylic acid (6b). Diester **6a** (45 mg, 0.144 mmol) was added to a solution of KOH (35.9 mg, 0.6 mmol) in aqueous MeOH (4 mL, 1:1, MeOH/H_2O) and the solution was stirred at rt for 2 h. The solution was then neutralized with 10% HCl as monitored by pH paper, inducing precipitation. The precipitate was collected by vacuum filtration and washed with water (3×2 mL), CH_2Cl_2 (2×2 mL), and dried in vacuo to give **6b** as a light gray solid (35.2 mg, 86%). Mp 143–145°C (dec.); IR (KBr): 3400–3250, 1734 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz), δ 8.43 (dd, J=7.9, 1.8 Hz, 2H), 7.64–7.56 (m, 3H); CIHRMS (NH_3,140 eV) m/z 285.0610 ($[M+1]^+$, calcd for $C_{13}H_9N_4O_4$ 285.0624).

4.1.3. 2-Phenyl-1*H*-imidazo[4,5-*d*]pyridazine (6c). *Method A:* Diacid **6b** (60 mg, 0.211 mmol) was dissolved in aqueous DMSO (4 mL, 1:1, DMSO/H_2O), and refluxed for 8.5 h. The solvent was removed in vacuo and the product purified by flash chromatography (EtOAc/MeOH, 25:2) to provide **6c** (36 mg, 87%) as a white solid. Mp 250–253°C (dec.); IR (NaCl): 3400–3000 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 9.09 (s, 2H), 8.29 (d, J=7.3 Hz, 2H), 7.37 (dd, J=7.3, 7.3 Hz, 2H), 7.28 (t, J=7.3 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 160.9, 140.5, 140.0, 130.7, 130.6,

128.8, 127.4; CIHRMS (butane, 140 eV) *m/z* 196.0749 ($[M]^+$, calcd for $C_{11}H_8N_4$ 196.0749).

Method B: Diester **5a** (70 mg, 0.357 mmol) was dissolved in HOAc and conc. HCl (6 mL, 1:1 HOAc/HCl), and refluxed for 3 h. The solvent was removed in vacuo, then the residue was redissolved in H_2O (5 mL) and the solution neutralized with 1 M aq KOH as monitored by pH paper. After evaporation of solvent, the residue was loaded onto a short silica gel column and eluted with EtOAc/MeOH (25:2) to give **6c** as a white solid (43.8 mg, 99+%).

4.1.4. Dimethyl 2-benzoylamino-1*H*-imidazo[4,5-*d*]pyridazine-4,7-dicarboxylate (6d). A solution of 2-aminoimidazole sulfate (681.1 mg, 2.5 mmol) was stirred in a solution of sodium carbonate (265 mg, 2.5 mmol) in water (3 mL) at rt for 15 min, then the water was evaporated in vacuo. The residue was slurried with anhydrous ethanol and filtered through Celite, and the solvent was removed in vacuo to give 2-aminoimidazole as an orange oil (391 mg, 94%).[24] To a solution of 2-aminoimidazole (33.2 mg, 0.4 mmol) in anhydrous THF (4 mL) was added Et_3N (0.17 mL, 1.2 mmol), DMAP (4.9 mg, 0.04 mmol) and benzoyl chloride (46.9 μL, 0.4 mmol), and the mixture was stirred at rt for 4 h. The precipitate which formed was removed by vacuum filtration, and the solvent removed in vacuo. The residual yellow solid was dissolved in anhydrous THF (5 mL), and tetrazine **4a** (79.2 mg, 0.4 mmol) was added. The reaction mixture was stirred at rt for 6 h under argon. After evaporation of the solvent, the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 25:2) to give **6d** (79.5 mg, 56%) as a yellow solid. Mp 217–219°C; IR (NaCl): 3362, 1726, 1702, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 12.5 (bs, NH), 11.4 (bs, NH), 7.94 (dd, *J*=7.9, 1.2 Hz, 2H), 7.61 (tt, *J*=7.6, 1.2 Hz, 1H), 7.43 (dd, *J*=7.9, 7.6 Hz, 2H); 4.19 (bs, 3H); 3.90 (bs, 3H); ^{13}C NMR (pyridine-d_5, solubility in $CDCl_3$ was too low for ^{13}C NMR, 67.5 MHz): δ 170.4, 165.2, 154.8, 141.1, 137.7, 134.2, 134.1, 129.7, 129.6, 53.4; CIHRMS (NH_3, 140 eV), *m/z* 356.0972 ($[M+1]^+$, calcd for $C_{16}H_{14}N_5O_5$ 356.0995).

4.1.5. 2-Amino-N^1-benzoylimidazole (3e). To a solution of 2-aminoimidazole (41.4 mg, 0.5 mmol) prepared as described above for **6d**[24] in anhydrous THF (8 mL) was added Et_3N (0.21 mL, 1.5 mmol), then benzoyl chloride (52.8 μL, 0.45 mmol). The reaction mixture was stirred overnight, then diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL), then the organic extracts dried over Na_2SO_4. No further purification was possible due to instability, and crude **3e**, judged to be 95% pure by ^1H NMR, was used in further steps. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.74–7.72 (m, 2H), 7.64–7.59 (m, 1H), 7.52–7.49 (m, 2H), 6.68 (d, *J*=2.4 Hz, 1H), 6.54 (d, *J*=2.4 Hz, 1H), 6.00 (bs, 2NH).

4.1.6. 2-[(Dimethylamino)methylene]aminoimidazole (3f). 2-Aminoimidazole sulfate (539.3 mg, 2.0 mmol) and sodium carbonate (212 mg, 2 mmol) were dissolved in water (4 mL) and stirred at rt for 15 min. Water was removed in vacuo, the residue dissolved in *N*,*N*-dimethylformamide dimethyl acetal (10 mL), and the suspension was stirred at rt overnight. After evaporation of solvent, the product was purified by flash chromatography (CH_2Cl_2/Et_3N, 20:1) to give **3f** as a white solid (524.5 mg, 95%). Mp 140–142°C; IR (NaCl): 3101, 1627 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 10.6 (bs, NH) 8.48 (s, 1H), 6.72 (s, 2H), 3.04 (s, 3H), 2.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.9, 152.8, 119.0 (br), 40.4, 34.5; EIHRMS (70 eV), *m/z* 138.0916 ($[M]^+$, calcd for $C_6H_{10}N_4$ 138.0905).

4.1.7. Dimethyl 2-[(dimethylamino)methylene]amino-1*H*-imidazo[4,5-*d*]pyridazine-4,7-dicarboxylate (6e). Protected 2-aminoimidazole **3f** (64 mg, 0.46 mmol) and tetrazine **4a** (115.4 mg, 0.583 mmol) under argon were mixed in anhydrous THF at −78°C. The temperature was allowed to slowly rise to rt over a 2 h period, then the mixture was stirred overnight. The solvent was removed in vacuo, then the product purified by flash chromatography (EtOAc/MeOH, 10:1) to give **6e** as a light yellow solid (121 mg, 86%). Mp 200–202°C; IR (NaCl) 3300–3000, 1734, 1632 cm^{-1}; ^1H NMR (CD_3OD, 400 Hz) δ 8.69 (s, 1H), 4.06 (s, 6H), 3.26 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (CD_3OD, 75 MHz, 50°C) δ 167.1, 165.6, 162.2, 140.9, 139.1, 53.5, 41.8, 35.6; CIHRMS (butane, 140 eV) *m/z* 307.1179 ($[M+1]^+$, calcd for $C_{12}H_{14}N_6O_4$ 307.1155).

4.1.8. 2-Amino-1*H*-imidazo[4,5-*d*]pyridazine (1). *Method A:* Diester **6d** (78 mg, 0.22 mmol) was dissolved in HOAc and conc HCl (4 mL, 1:1), and refluxed for 3 h. The solvent was removed in vacuo, and the residue redissolved in H_2O (5 mL), then the solution was neutralized with 1 M aqueous KOH as monitored with pH paper. After evaporation of the solvent, the residue was loaded onto a short silica gel column and eluted with EtOAc/MeOH (5:1) to give **1** as a white solid (29 mg, 98%). Mp 220–230°C (dec.); IR (KBr): 3400 cm^{-1}; UV (MeOH) λ_{max} (log ε) 206 (4.22), 230 (sh), 262 (3.71), 308 (sh); (+NaOH) 216 (4.29), 272 (3.66); ^1H NMR (D_2O, 400 MHz) δ 8.80 (bs, 2H); (DMSO-d_6, 400 MHz) δ 11.5 (bs, NH), 8.94 (bs, 2H), 6.97 (bs, NH_2); ^{13}C NMR (D_2O, CD_3OD as internal reference, 75 MHz) δ 169.6, 145.9, 139.1 (DMSO-d_6, 75 MHz) δ 159.9, 138.8, 136.1; EIHRMS (70 eV) *m/z* 135.0535 ($[M]^+$, calcd for $C_5H_5N_5$ 135.0545). The HCl salt of **1** was made as follows. To a solution of the free base was added 10% aq. HCl to pH<1. The solvent was removed to give a white solid. Mp>300°C (dec); UV (MeOH) λ_{max} (log ε) 206 (4.26), 225 (sh), 262 (3.76), 306 (2.84); (+HCl) 210 (4.05), 268 (3.62), 292 (3.71); ^1H NMR (DMSO-d_6, 400 MHz) δ 9.26 (bs, 2H), 8.20 (bs, NH_3); ^{13}C NMR (DMSO-d_6, 67.5 MHz, 50°C) δ 161.9, 140.7, 132.8.

Method B: Diester **6e** (60 mg, 0.196 mmol) was dissolved in HOAc and conc HCl (4 mL, 1:1), and refluxed for 3 h. The solvent was removed in vacuo, and the residue redissolved in H_2O (4 mL), then the solution was neutralized with 1 M aqueous KOH as monitored with pH paper. After evaporation of the solvent, the residue was loaded onto a short silica gel column and eluted with EtOAc/MeOH (5:1) to give **1** as a white solid (26 mg, 98%).

4.1.9. 1*H*-Imidazo[4,5-*d*]pyrazine (8). Beginning with 2,3-dichloropyrazine, copper-promoted amination produced 2,3-diaminopyrazine, which was condensed with triethyl orthoformate to give **8**.[32a]

4.1.10. 1-Methoxymethylimidazo[4,5-*b*]pyrazine (9a). To a solution of imidazo[4,5-*b*]pyrazine (**8**, 180 mg, 1.5 mmol) in anhydrous THF (10 ml) under argon was added Et_3N (0.63 ml, 4.5 mmol) at 0°C, then MOMCl (0.165 ml, 1.65 mmol) was added dropwise. The ice bath was removed and the mixture stirred at rt for 3 h. The precipitate was removed by filtration, and washed with methylene chloride (3×20 mL). The solvent was removed from the filtrate in vacuo and the residue purified by flash chromatography (Et_3N/hexanes/EtOAc, 1:50:100) to give **9a** as a light yellow solid (227 mg, 92%). Mp 54–57°C; ^{1}H NMR ($CDCl_3$, 400 Hz) δ 8.56 (d, J=2.9 Hz, 1H), 8.46 (s, 1H), 8.37 (d, J=2.9 Hz), 5.63 (s, 2H); 3.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.9, 147.0, 140.6, 140.0, 139.1, 74.5, 57.3; EIHRMS (70 eV) m/z 164.0704 ($[M]^+$, calcd for $C_7H_8N_4O$ 164.0698).

4.1.11. 1-Benzyloxymethylimidazo[4,5-*b*]pyrazine (9b). The compound was prepared according to the procedure above for **9a** from imidazo[4,5-*b*]pyrazine (**8**, 120 mg, 1.0 mmol), with Et_3N (0.42 mL, 3.0 mmol) and BOMCl (0.35 mL, 1.5 mmol). Purification by flash chromatography (Et_3N/hexanes/EtOAc, 1:50:100) gave **9b** as a light yellow solid (230 mg, 96%). Mp 79–81°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.58 (d, J=2.5 Hz, 1H), 8.46 (s, 1H), 8.39 (d, J=2.5 Hz, 1H), 7.33–7.25 (m, 5H), 5.74 (s, 2H), 4.60 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.9, 147.0, 140.5, 139.9, 138.9, 136.1, 128.4 (2C), 128.2 (2C), 127.7, 72.3, 71.8; EIHRMS (70 eV) m/z 240.0998 ($[M]^+$, calcd for $C_{13}H_{12}N_4O$ 240.1011).

4.1.12. 1-(4-Nitrobenzyl)imidazo[4,5-*b*]pyrazine (9c). A suspension of imidazo[4,5-*b*]pyrazine (**8**, 36 mg, 0.3 mmol), Ag_2O (69 mg, 0.3 mmol) and 4-nitrobenzylbromide (78.6 mg, 0.36 mmol) in benzene (6 mL) was refluxed for 5 h. Anhydrous CH_2Cl_2 (3×20 mL) was added and the precipitate was removed by filtration. The solvent was removed in vacuo and the residue purified by flash chromatography (EtOAc) to give **9c** as a yellow solid (38 mg, 50%, unoptimized). Mp 190–192°C; ^{1}H NMR ($CDCl_3$, 400 Hz) δ 8.59 (d, J=2.6 Hz, 1H), 8.38 (s, 1H), 8.36 (d, J=2.6 Hz, 1H), 8.20 (d, J=8.6 Hz, 2H), 7.46 (d, J=8.6 Hz, 2H), 5.58 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.8, 148.2, 146.4, 141.9, 140.8, 139.7, 139.2, 128.6 (2C), 124.4 (2C), 47.0; EIHRMS (70 eV) m/z 255.0761 ($[M]^+$, calcd for $C_{12}H_9N_5O_2$ 255.0756).

4.1.13. 1-Triphenylmethylimidazo[4,5-*b*]pyrazine (9d). A suspension of imidazo[4,5-*b*]pyrazine (**8**, 60 mg, 0.5 mmol), K_2CO_3 (207 mg, 1.5 mmol) and triphenylmethylchloride (209.1 mg, 0.75 mmol) in anhydrous DMF was stirred at rt for 6 h. After removal of the precipitate by filtration, solvent was removed from the filtrate in vacuo and the residue purified by flash chromatography (hexanes/EtOAc, 1:2) to give **9c** as a white solid (99 mg, 55%, unoptimized yield). Mp 196–198°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40 (d, J=2.7 Hz, 1H), 8.33 (s, 1H), 8.05 (d, J=2.7 Hz, 1H), 7.29–7.25 (m, 9H), 7.17–7.14 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.7, 147.9, 141.1, 140.7 (3C), 139.9, 138.4, 129.6 (6C), 128.1 (6C), 128.0 (3C), 76.3; EIHRMS (70 eV) m/z 362.1555 ($[M]^+$, calcd for $C_{24}H_{19}N_4$ 362.1551).

4.2. General procedure for azidation of protected imidazo[4,5-*b*]pyrazines 9a and 9b

To a solution of the title compounds in anhydrous toluene at −78°C, was added freshly prepared LDA (1.2 equiv.) in anhydrous THF with stirring. Stirring was continued at −78°C for 20 min, then TsN_3 (1.5 equiv.) in toluene was added rapidly. The temperature was allowed to rise to rt over a one to two hour period, then the reaction was quenched with saturated aq. $NaHCO_3$, (10 mL), extracted with CH_2Cl_2 (3×20 mL), and the organic layer dried with Na_2SO_4. After decanting from the Na_2SO_4, the solvent was removed in vacuo and the residue purified by flash chromatography.

4.2.1. 2-Azido-1-methoxymethylimidazo[4,5-*b*]pyrazine (10a). This compound was synthesized according to the general procedure from 1-methoxymethylimidazo[4,5-*b*]pyrazine (**9a**, 145 mg, 0.88 mmol in 25 mL toluene) with LDA (1.06 mmol in 4 mL THF) and TsN_3 (261.2 mg, 1.32 mmol in 2 mL toluene). Purification by flash chromatography (Et_3N/hexanes/EtOAc, 1:50:50) gave **10a** as a light yellow oil which solidified upon standing (104 mg, 57%). Mp 91–93°C; IR (NaCl) 2173, 2138 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.39 (d, J=2.9 Hz, 1H), 8.16 (d, J=2.9 Hz, 1H), 5.44 (s, 2H), 3.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 153.2, 148.2, 141.2, 140.1, 137.3, 72.3, 57.6; EIHRMS (70 eV) m/z 205.0722 ($[M]^+$, calcd for $C_7H_7ON_7$ 205.0712). The dimer **11a** was also isolated as a yellow solid (45 mg, 16%). Mp 241–242°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.68 (d, J=2.4 Hz, 1H), 8.53 (d, J=2.4 Hz, 1H), 6.54 (s, 2H), 3.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.7, 145.2, 142.2, 141.5, 141.1, 74.7, 57.5; EIHRMS (70 eV) m/z 326.1255 (30%, $[M]^+$, calcd for $C_{14}H_{14}O_2N_4$ 326.1239).

4.2.2. 2-Azido-1-benzyloxymethylimidazo[4,5-*b*]pyrazine (10b). This compound was synthesized according to the general procedure from 1-benzyloxymethylimidazo[4,5-*b*]pyrazine (**9b**, 162 mg, 0.675 mmol in 20 mL toluene), with LDA (0.81 mmol in 3 mL THF) and TsN_3 (200 mg, 1.01 mmol in 2 mL toluene). Purification by flash chromatography (Et_3N/hexanes/EtOAc, 1:50:50) gave **10b** as a yellow oil (131 mg, 69%). IR (NaCl) 2166, 2130 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41 (d, J=2.9 Hz, 1H), 8.19 (d, J=2.9 Hz, 1H), 7.31–7.23 (m, 5H), 5.56 (s, 2H), 4.62 (s, 2H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 153.1, 148.2, 141.0, 140.0, 137.2, 136.5, 128.4, 128.1, 127.6, 72.1, 70.5; EIHRMS (70 eV) m/z 281.1002 ($[M]^+$, calcd for $C_{13}H_{11}ON_7$ 281.1025). The dimer **11b** was also isolated as a yellow solid (36 mg, 11%). Mp 241–242°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.67 (d, J=2.4 Hz, 1H), 8.53 (d, J=2.4 Hz, 1H), 7.13 (bs, 5H), 6.60 (s, 2H), 4.68 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.7, 145.1, 142.1, 141.3, 141.0, 136.9, 128.2 (2C), 127.8, 127.5 (2C), 73.0, 72.0; CIHRMS (NH_3, 140 eV) m/z 479.1948 ($[M+1]^+$, calcd for $C_{26}H_{23}O_2N_8$ 479.1943).

4.3. General procedure for the reduction of azides 10a and 10b

The azide was mixed with Pd–C (30–50 wt%) in MeOH in a round-bottom flask sealed with a septum. A balloon filled

with H_2 was fitted through the septum, the flask was briefly purged with H_2, and the reaction mixture stirred at rt for 2 h. The mixture was filtered through a pad of Celite, to remove the catalyst, and the solvent removed from the filtrate in vacuo to give the product amine, which could be directly deprotected without further purification. Purification could be accomplished by filtering through a silica gel plug eluting with MeOH/EtOAc (1:20).

4.3.1. 2-Amino-1-methoxymethylimidazo[4,5-*b*]pyrazine (12a). This compound was synthesized according to the general procedure from 2-azido-1-methoxymethylimidazo[4,5-*b*]pyrazine (**10a**, 50 mg, 0.24 mmol) and Pd–C (25 mg) in MeOH (10 mL) to give **12a** as an off-white solid (43 mg, 99+%). Mp 203–205°C; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.99 (d, J=2.7 Hz, 1H), 7.85 (d, J=2.7 Hz, 1H), 5.47 (s, 2H), 3.46 (s, 3H); ^{13}C NMR (CD_3OD, 67.5 MHz) δ 160.4, 151.8, 143.5, 137.8, 134.0, 73.0, 57.2; EIHRMS (70 eV) m/z 179.0792 ($[M]^+$, calcd for $C_7H_9ON_5$ 179.0807).

4.3.2. 2-Amino-1-benzyloxymethylimidazo[4,5-*b*]pyrazine (12b). This compound was synthesized according to the general procedure from 2-azido-1-benzyloxymethylimidazo[4,5-*b*]pyrazine (**10b**, 65 mg, 0.23 mmol) and Pd–C (20 mg) in MeOH (8 mL) to give **12b** as an off-white solid (43 mg, 99+%). Mp 136–138°C; ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.03 (d, J=2.9 Hz, 1H), 7.83 (d, J=2.9 Hz, 1H), 7.36–7.24 (m, 5H), 7.06 (bs, NH_2), 5.67 (s, 2H), 4.64 (s, 2H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 159.4, 152.2, 142.8, 138.6, 138.3, 133.4, 129.2 (2C), 128.8 (2C), 128.7, 71.7, 70.9; EIHRMS (70 eV) m/z 255.1096 ($[M]^+$, calcd for $C_3H_{13}ON_5$ 255.1120).

4.3.3. 2-Amino-1*H*-imidazo[4,5-*b*]pyrazine (2). *Method A:* 2-Amino-1-methoxymethylimidazo[4,5-*b*]pyrazine (**12a**, 40 mg, 0.23 mmol) was dissolved in MeOH (10 mL) and 10% aq. HCl (10 mL) and heated to reflux for 10 h. The solvent was removed in vacuo, the precipitate was washed with anhydrous acetone. The residue was redissolved in MeOH and neutralized with 1% KOH as monitored by pH paper. After the removal of solvent, the crude product was filtered through a silica gel plug eluting with Et_3N/MeOH/$CHCl_3$ (1:2:6) to give **2** as a white solid (33.3 mg, 99+%). The product can be recrystallized from either H_2O or MeOH. Mp>300°C (dec.); IR (KBr): 3400 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 217 (sh), 244 (3.30), 318 (4.03); (+NaOH) 206 (4.31), 230 (sh), 282 (sh), 326 (3.59); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.74 (bs, NH), 7.78 (bs, 2H), 7.12 (bs, NH_2); ^{13}C NMR (DMSO-d_6, 67.5 MHz, temp=50°C) δ 158.7, 146.9, 133.4; EIHRMS (70 eV) m/z 135.054 ($[M]^+$, calcd for $C_5H_5N_5$ 135.0545). The HCl salt of **2** was made as follows. To a solution of the free base was added 10% aq. HCl to pH<1. The solvent was removed to give a white solid; mp>300°C (dec.); UV (MeOH) λ_{max} (log ϵ) 217 (sh), 244 (3.62), 318 (4.39); (+HCl) 204 (3.89), 218 (sh), 274 (sh), 306 (4.07), 340 (sh); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.79 (bs, NH_3), 8.09 (bs, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz, temp=50°C) δ 155.0, 141.6, 131.9.

Method B: To a solution of 2-amino-1-benzyloxymethylimidazo[4,5-*b*]pyrazine (**12b**, 50 mg, 0.2 mmol.) in anhydrous toluene (10 mL) at 0°C was added BBr_3 (1 M in toluene, 1.2 ml, 1.2 mmol) dropwise. The reaction mixture was stirred at rt for 1.5 h, then anhydrous MeOH (10 mL) was added and stirring continued for 20 min. The solvent was removed in vacuo, the residue was washed with anhydrous acetone, then redissolved in MeOH, and neutralized with 1% KOH. Purification as above gave **2** as a white solid (24 mg, 89%).

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