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Synthesis of Fused Imidazole-Containing Ring Systems *via* Dual Oxidative Amination of C(sp^3)-H bonds.

Georgette Castanedo,* Yanzhou Liu, James J. Crawford and Marie-Gabrielle Braun

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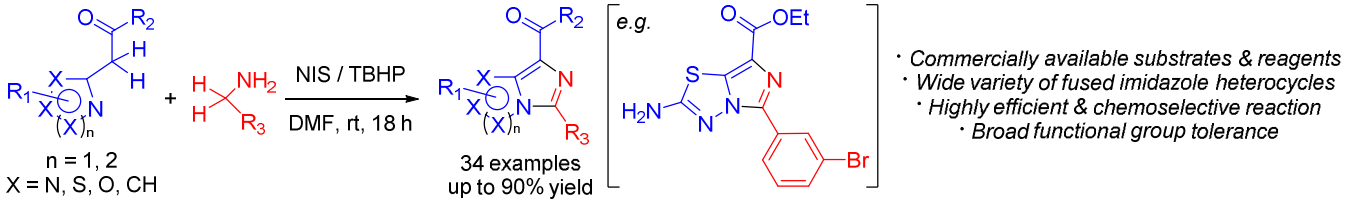
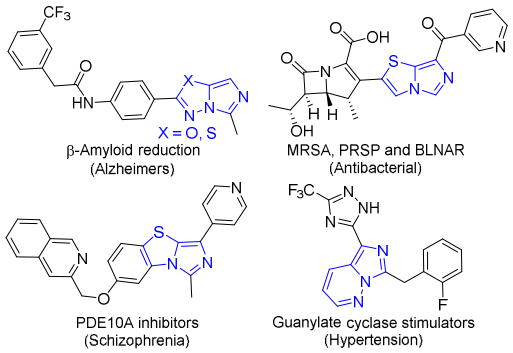


ABSTRACT: A general and efficient method for a metal-free one-pot synthesis of highly substituted fused imidazole containing 5,5 and 5,6 fused bicyclic heterocycles is described. Starting from commercially available substrates and reagents, the reaction proceeds through two C–N bond formations and an oxidative dehydrogenation to form highly substituted products in good to excellent yield.

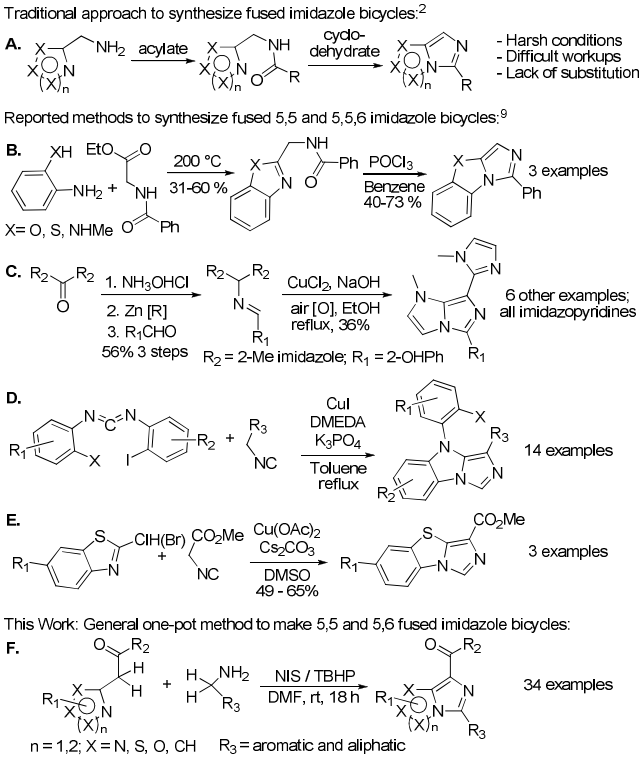
Fused heterocyclic ring systems containing bridgehead nitrogens are not only biologically relevant but are valuable building blocks in medicinal chemistry and present a persistent synthetic challenge (Figure 1).[1] Typical approaches to their synthesis involve acylation of ortho-nitrogen containing arylmethylamines and subsequent cyclodehydration (Scheme 1, **A**.).[2] Several recent publications have reported routes to poly-substituted 5,6 fused imidazo[1,5-*a*]pyridines in one pot through CH arylation,[3] multi-component condensation[4] and C(sp^3)-H amination,[5-8] however methods to access 5,5 and 5,5,6 fused ring systems remain scarce and often suffer from limitations such as lack of commercial availability of starting materials, long synthetic routes, harsh reaction conditions, complex isolation procedures and limitations in scope (Scheme 1, **B-E.**).[9]

Figure 1 Examples of fused imidazole-containing rings in medicinal chemistry[1]



In the course of one of our medicinal chemistry programs, we became interested in testing the effect of replacing an imidazo[1,5-*a*]pyridine core with a variety of 5,5 fused bridgehead nitrogen containing heterocycles. In studying the existing methods, we found a number of inadequacies including the aforementioned drawbacks. We envisioned that a general method to synthesize 5,5 imidazole containing fused ring systems would be valuable from both a synthetic as well as a medicinal chemistry perspective. Herein we report a robust and chemoselective method for their synthesis in a one-pot fashion from commercially available starting materials (Scheme 1, **F.**).

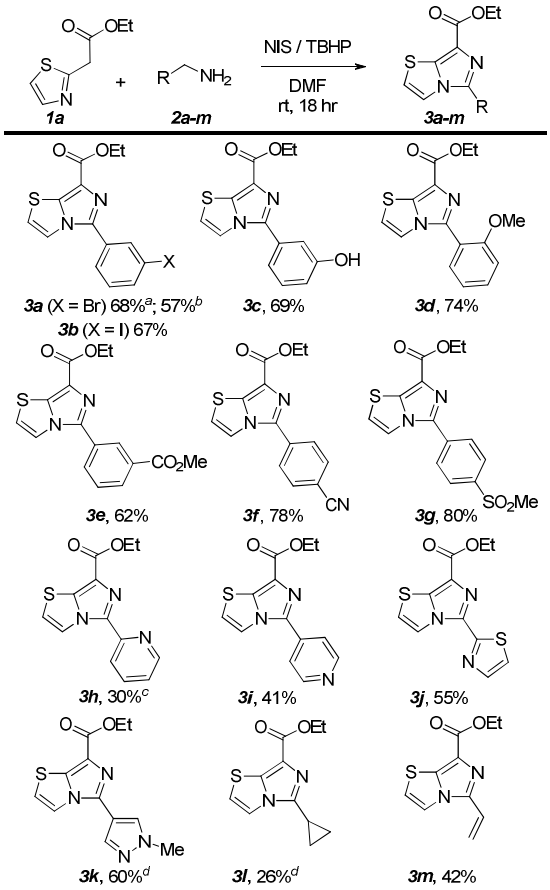
Scheme 1. Summary of Methods to Synthesize Fused Imidazole Ring Systems



Pioneering work by Yan et al. demonstrated the first example of a metal-free sequential dual oxidative amination of C(sp^3)-H bonds to synthesize imidazo[1,5-*a*]pyridines.[5] With this as a foundation, we sought to optimize the transformation to be applicable for the synthesis of a broad range of fused ring systems. At the outset of our investigation, we were able to demonstrate that the reaction could be performed in standard vials, negating the requirement for a Schlenk tube and making it more experimentally convenient.[5] We found that the order of addition was also important, with the best results obtained when the iodine source and oxidant were added to a solution of heteroaromatic substrate and amine in solvent.[10] With these adjustments in place, we began our evaluation of the reaction conditions (see SI, Table 1). Beginning with ethyl 2-(thiazol-2-yl)acetate (***1a***, 1.0 equiv), 3-bromobenzylamine (***2a***, 2.0 equiv), iodine source (1.0 equiv) and TBHP (3.0 equiv) in DMA (0.5 M), we were pleased to observe formation of ethyl 5-(3-bromophenyl)imidazo[5,1-*b*]thiazole-7-carboxylate ***3a*** as the primary product. Furthermore, NIS appeared to be the best iodine source of those screened for 5,5 fused ring formation. In

our examination of the effect of solvent (see SI, Table 2), we found that ACN was marginally better in terms of yield of ***3a,*** but ultimately DMF was selected because of its superior solubilizing ability. With our newly optimized conditions in hand, we proceeded to probe the amine scope (Table 1).

Table 1: Amine Scope of imidazo[5,1-*b*]thiazole core



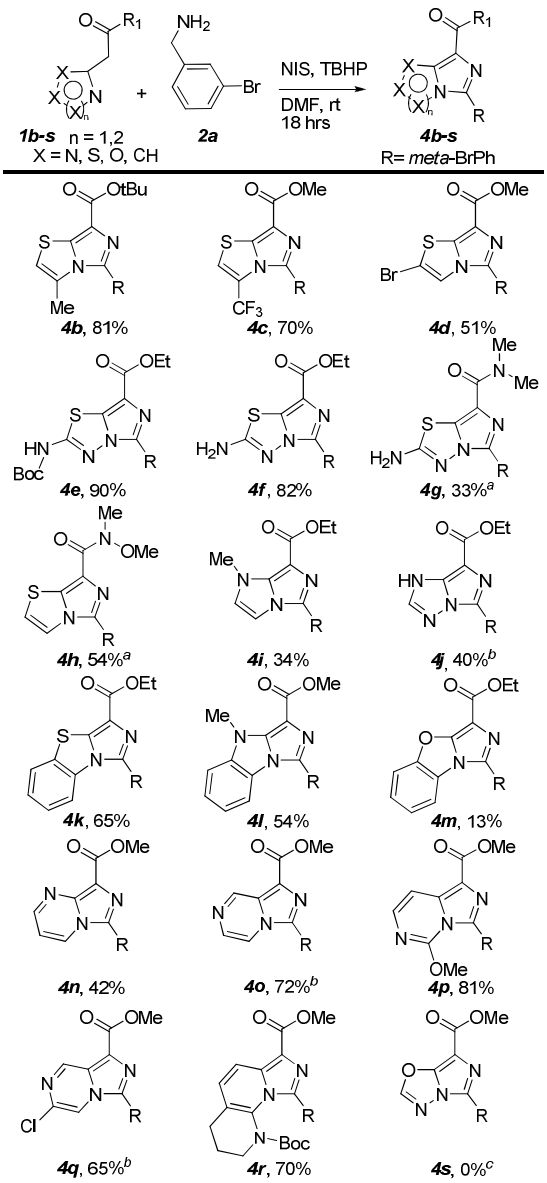
Isolated % yields reported. Reaction conditions: ***1a*** (0.5 mmol), ***2*** (1.0 mmol), NIS (0.5 mmol), TBHP (1.5 mmol), Solvent (0.5 M), rt, 18 h. [a] ACN as solvent, [b] 0.5 mmol and 6.0 mmol scale in DMF gave same yield, [c] 1.1 equiv of amine, [d] Reaction heated at 80 °C for 18 h.

Compound ***3a*** was isolated in 68% yield in ACN and 57% yield in DMF with no column purification, with the product isolated following trituration of the reaction mixture.[11] We were able to demonstrate the scalability of the reaction by achieving the same yield (57%) at 1 gram (6 mmol) scale in DMF. The method tolerates both electron-donating (hydroxy ***2c***, methoxy ***2d***) and electron-withdrawing groups on the amine (halogens ***2a*** and ***2b***, ester ***2e***, nitrile ***2f*** and sulfone ***2g***). Examples ***3a*** and ***3b*** contain halogens that can act as a synthetic handle for further elaboration. We were very gratified to see that the free hydroxyl group in ***3c*** was benign under the reaction conditions.[12] The *ortho*-methoxy substituent in ***3d*** demonstrated that the

reaction can also tolerate increased steric demand on the amine substrate.[13] The exceptional chemoselectivity and functional group tolerability of the reaction was further evidenced by examples ***3e-g***, where an ester, nitrile and sulfone were not affected under these reaction conditions. Interestingly, amine substrates ***2h–k*** with additional potentially reactive nitrogens were also tolerated in the reaction (examples ***3h–k***). Although pyridin-2-ylmethanamine had not been demonstrated as a viable amine substrate on prior occasions with similarly proposed mechanisms,[6,8,14] the corresponding product, ***3h***, was obtained, albeit in low yield, through adjusting the number of equivalents of the amine substrate from 2.0 to 1.1. The scope was further expanded to include aliphatic amines as in ***3l*** and ***3m***. In addition, the allylic moiety in ***3m*** is a multifaceted group that is poised to undergo further functionalization. Although the isolated yields were somewhat low for several of the examples in this table, we were delighted to synthesize a wide variety of highly complex, poly-substituted imidazo[5,1-*b*]thiazoles with exceptional chemoselectivity and diversity in one step with broad functional group tolerance.[15]

Our attention then turned to investigating the scope of heteroaromatic substrate (Table 2). Electron-donating and withdrawing groups (Me, CF_3, Br) were tolerated at multiple positions on the imidazo[5,1-*b*]thiazole as seen in examples ***4b–d***. Initially we chose to mask the free amino group of the heteroaromatic substrate in ***4e*** with a *tert*-butoxycarbonyl (Boc) group as we were concerned that it might hinder product formation. We were subsequently able to show that this is not the case, as the free amino group was tolerated under the reaction conditions as shown by ***4f*** and ***4g***. Additionally, we were unable to find any prior instances of this imidazo[5,1-*b*][1,3,4]thiadiazol-2-amine core in the literature. The Weinreb amide was also a competent substrate in this reaction shown by ***4h*** in 54% yield and is a versatile handle for additional manipulation. Furthermore, the tertiary amide ***4g*** can potentially be readily converted to an aldehyde.[16] Imidazo[1,5-*a*]imidazole ***4i*** was lower yielding at 34% but our one-step synthesis, which allowed for more structural diversification, offered advantages over the previously reported 4-step method to make this ring system.[9e] Similarly, the poly-substituted imidazo[1,5-*b*][1,2,4]triazole ***4j***, whose starting material and subsequent product contains a free NH, was poorly exemplified in the literature but easily prepared in 40% yield with this method.[17] As demonstrated by ***4k–m***, benzothiazole, benzimidazole and benzoxazole were all competent substrates in the reaction to form the corresponding fused 5,5,6 ring systems. In some cases, low yields can be potentially be explained by the pK_a of the nitrogen in the heteroaromatic substrate, which offers a relative estimation of its nucleophilicity. In particular, for methyl 2-(benzo[*d*]oxazol-2-yl)acetate (***1m***), used to synthesize ***4m*** in 13% yield, the pK_a is on the order of 0.5.[18] Several other examples of heteroaromatic substrates whose nitrogen atom has a negative or unknown pK_a value failed to yield any product (such as isoxazole, 1,2,4-oxadiazole and benzo[*d*]isothiazole).[19] We were able to observe formation of imidazo[5,1-*b*][1,3,4]oxadiazole ***4s*** but it rapidly decomposed during isolation, presumably due to instability of the product.[20]

Table 2: Heteroaromatic Substrate Scope



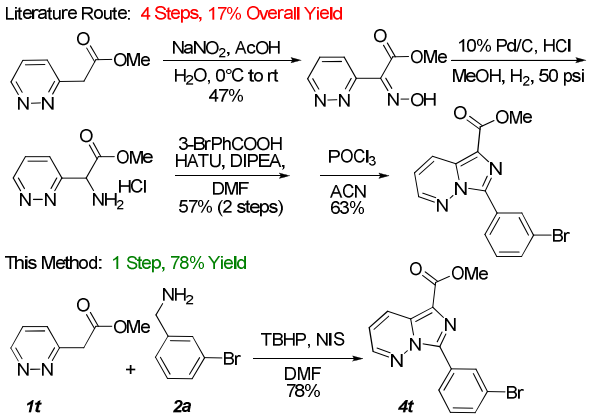
Isolated % yields reported. Reaction conditions: ***1*** (0.5 mmol), ***2a*** (1.0 mmol), NIS (0.5 mmol), TBHP (1.5 mmol), Solvent (0.5 M), rt, 18 hrs. [a] Reaction heated at 80 °C for 18 h [b] 1.1 eq of amine used, [c] Product was observed but not isolated due to rapid decomposition.

After demonstrating the successful synthesis of a variety of complex fused 5,5 and 5,5,6 imidazole-containing bicycles, we wanted to further demonstrate the robustness of the method through extension to fused 5,6 systems.[21] To that end, with examples ***4n–r***, we were able to show that highly substituted 5,6 fused imidazole ring systems including imidazo[1,5-*a*]pyrimidine, imidazo[1,5-*a*]pyrazine, imidazo[1,5-*c*]pyrimidine and 1,2,3,4-tetrahydroimidazo[1,5-*a*][1,8]naphthyridine

could all be accessed using this method. Although the one-pot synthesis of the imidazo[1,5-*c*]pyrimidine core was not compatible with a prior method,[14] we were gratified to isolate ***4p*** in 81% yield. In addition, ***4q*** demonstrated that a reactive functional group (chlorine) on the pyrazine substrate remained undisturbed, and offered an option for further elaboration if necessary.

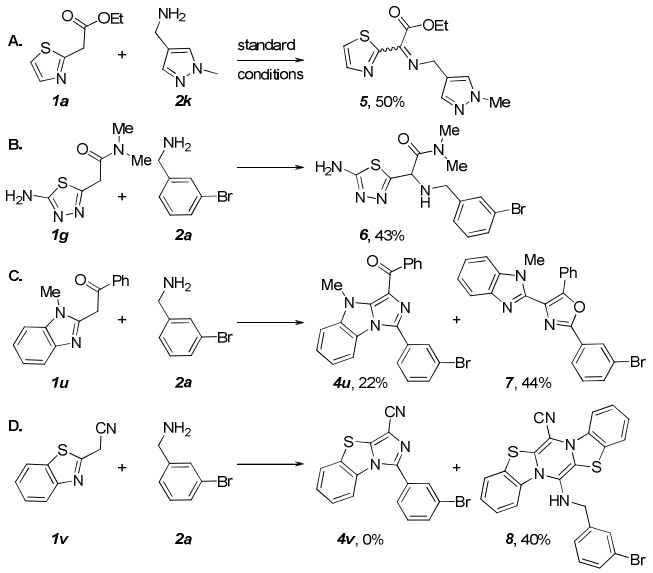
In addition to displaying the broad scope of the amine and heteroaromatic substrates, we were able to use this methodology to improve upon a synthesis of an imidazo[1,5-*b*]pyridazine intermediate that had been employed in the synthesis of NF-κβ inducing kinase (NIK) inhibitors (Scheme 2).[1d] Using methyl-2-pyridazin-3-yl)acetate ***1t*** as a common starting material, ***4t*** was synthesized in 78% yield following a trituration, avoiding any column chromatography, rather than in 4 steps and 17% overall yield with the previous literature route.

Scheme 2. Improved Route to Literature Intermediate (Example *4t*)[1d]



With the objective of further elucidating the reaction mechanism, we isolated and characterized several reaction intermediates encountered during our scope investigations. Imine intermediate ***5*** was obtained in 50% yield when the reaction was performed at room temperature (Scheme 3, **A.**), but conversion to product ***3k*** (Table 1) could be effected with heating to 80 °C from the outset. Similarly, secondary amine ***6*** was isolated in 43% yield (Scheme 3, **B.**), while formation of product ***4g*** (Table 2) was realized when the reaction was heated to 80 °C.[22] The isolation of both imine ***5*** and secondary amine ***6*** as reaction intermediates support the previously reported proposed mechanistic pathways.[5,8,13,23] We also observed when the heteroaromatic substrate was a ketone and the starting material was primarily in the enol form (as indicated by NMR), preferential and unexpected formation of a 2,4,5 substituted oxazole ***7*** was seen in 44% yield over our desired imidazobenzimidazole ***4u,*** obtained in 22% yield (Scheme 3, **C.**). We are currently investigating whether we can alter the conditions to bias the reaction outcome. In addition, mechanistic studies are underway in an attempt to elucidate the reaction mechanism beyond what has been previously reported.

Scheme 3. Isolated Potential Reaction Intermediates and By-Products



Isolated % Yields Reported. Standard Reaction Conditions: ***1*** (0.5 mmol), ***2*** (1 mmol), NIS (0.5 mmol), TBHP (1.5 mmol), Solvent (0.5 M), rt, 18 h.

Attempts to expand the scope beyond ester, ketone, amide and Weinreb amide moieties at C–4 of the imidazole ring met with some limitations. In the case of the nitrile, instead of ***4v***, we saw the benzo[*d*]thiazole ring nitrogens react preferentially over the secondary amine nitrogen to give ***8*** in 40% yield (Scheme 3, **D.**).[24] Additional heteroaromatic substrates containing electron withdrawing groups such as CF_3, SO_2Ph and symmetrical benzo[*d*]thiazole rings (with CH_2 in between) also failed to give product, which we attributed to insufficient captodative resonance stabilization of the proposed radical reaction intermediate.[5,8,14]

In summary, we were able to develop a highly chemoselective, robust, and general method to synthesize a variety of historically difficult to access, complex poly-substituted fused 5,5 and 5,6 imidazole containing heterocycles in moderate to excellent yields. A wide array of functional group tolerance on both the heteroaromatic and amine substrates was demonstrated. Additionally, our method allowed access to fused heterocycles which had not been previously reported in the literature. We believe this method has the capability of being impactful in such fields as medicinal chemistry, agrochemicals and materials as it allows for rapid synthesis of a diverse range of fused heterocycles.

EXPERIMENTAL SECTION

General Information. Unless otherwise indicated, all commercial reagents and solvents were used without additional purification. Anhydrous solvents were used in reaction optimization and scope. ^{1}H-NMR spectra were recorded with a 400 or 500

spectrometer. Chemical shifts (in ppm) were referenced to tetramethylsilane (δ = 0 ppm) in DMSO-d_6 or $CDCl_3$ as an internal standard (2.5 or 7.26 ppm). ^{13}C-NMR spectra were obtained by the same NMR spectrometer and were calibrated with DMSO-d_6 or $CDCl_3$ (δ = 39.51 or 77.2 ppm). HRMS was recorded on an Orbitrap Q Exactive mass spectrometer. In situations where final compounds contain Bromine, ^{79}Br with the exact mass of 78.9183 was used in the calculation. Thin-layer chromatograms were performed on Silica gel 60 F254 aluminum-backed plates and visualized with UV light. Reactions were monitored by walkup a LCMS/UV system using 2-98% acetonitrile/0.1% formic acid (or 0.01% Ammonia) over 2.5 min (short method) or 5.5 min (long method). Flash column chromatography purifications were performed on automated systems equipped with 254 and 280 nm wavelengths. Reverse phase purification of compound ***4m*** was carried out by HPLC with a gradient of 5−95% acetonitrile/water (with 0.1% formic acid or 0.1% NH_4OH) over 10 min at 60 mL/min. The starting materials were commercially available with the exception of ***1e***, ***1h***, ***1p*** and ***1q***. Ethyl 2-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)acetate used in synthesis of compound ***4l*** was prepared as described in Chapman, D.D.; Elwood, J.K.; Hesltine, D.W.; Hess, H.M.; Kurtz, D.W. *J. Org. Chem*., **1977**, *42*, 2474.

General Procedure A. To a stirring solution of the heteroaromatic substrate (0.5 mmol) in *N,N*-dimethylformamide (2 mL/mmol, 0.5 M) was added the benzylamine derivative (1.0 mmol, 2.0 equiv), NIS (0.5 mmol, 1.0 equiv) and finally TBHP (70% aq, 1.5 mmol, 3.0 equiv) dropwise. The reaction mixture was subsequently stirred overnight (18 hours) whereupon it was quenched by a saturated $Na_2S_2O_3$ solution (2.0 mL) to reduce any excess iodine followed by addition of a saturated ammonium chloride solution (10 mL) and extraction with dichloromethane (10 mL). The organic layer was dried with magnesium sulfate, filtered and concentrated to afford crude fused imidazole bicyclic product which was purified via flash column chromatography using a heptanes/iPrOAc or 3:1 iPrOAc:MeOH to heptanes gradient.

General Procedure B. Changes from above procedure as follows: After quenching reaction with a saturated $Na_2S_2O_3$ solution, a solid precipitated from the aqueous solution which was further diluted with water (10 mL), collected by filtration and triturated by sonicating or rinsing the solid in a slurry of methanol. The solid was re-collected by filtration and dried under vacuum to afford pure fused imidazole bicyclic product without the necessity of column purification.

Ethyl 2-[5-(*tert*-butoxycarbonylamino)-1,3,4-thiadiazol-2-yl]acetate (***1e***). To a suspension of ethyl 2-(5-amino-1,3,4-thiadiazol-2-yl)acetate (500 mg, 2.67 mmol, 1.0 equiv) in dichloromethane (0.25 M, 10.7 mL) at room temperature was added di-*tert*-butyl dicarbonate (661 mg, 1.1 equiv,) and 4-dimethylaminopyridine (34 mg, 0.1 equiv). After stirring 18 h at room temperature, the reaction mixture was washed with 1 N HCI and the organic layer was dried with magnesium sulfate, filtered and concentrated. The crude was purified *via* flash column chromatography using a heptanes:iPrOAc gradient to afford 430 mg (56%) of ethyl 2-[5-(*tert*-butoxycarbonylamino)-1,3,4-thiadiazol-2-yl]acetate as a white solid ^{1}H NMR (400

MHz, DMSO-d_6) δ 11.81 (s, 1H), 4.19 – 4.11 (m, 4H), 1.49 (s, 9H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.8, 161.6, 156.2, 152.7, 81.9, 61.1, 35.0, 27.8, 14.0. HRMS (ESI) $[M+H]^+$ calc. $C_{11}H_{18}N_3O_4S$: 288.1018, found: 288.1013.

N-methoxy-*N*-methyl-2-thiazol-2-yl-acetamide (***1h***). To a solution of 2-thiazoleacetic acid (400 mg, 2.68 mmol, 1.0 equiv) in DMF (0.5 M) was added *N,O*-dimethylhydroxylamine hydrochloride (2.0 equiv), HATU (1.1 equiv) and DIPEA (4.0 equiv). The reaction was stirred for 30 minutes and quenched with a saturated ammonium chloride solution then extracted with DCM. The organic layer was dried with magnesium sulfate, filtered and concentrated and purified by column chromatography using a heptanes:iPrOAc gradient to afford 450 mg (90%) of *N*-Methoxy-*N*-methyl-2-thiazol-2-yl-acetamide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 3.4 Hz, 1H), 7.30 (d, J = 3.3 Hz, 1H), 4.24 (s, 2H), 3.74 (s, 3H), 3.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 162.8, 142.1, 120.0, 61.7, 36.6, 32.4. HRMS (ESI) $[M+H]^+$ calc. $C_7H_{11}N_2O_2S$: 187.0541, found: 187.0536.

Methyl 2-(2-methoxypyrimidin-4-yl)acetate (***1p***). To a 0.5 M solution of methyl 2-(2-chloropyrimidin-4-yl)acetate (460 mg, 2.5 mmol, 1.0 equiv) in MeOH (0.5 M) was added sodium methoxide (2.0 equiv, 30% mass in MeOH). The reaction was stirred for 24 hours at room temperature, then diluted with a saturated ammonium chloride solution (20 mL) and extracted with DCM (20 mL). The organic layer was dried with magnesium sulfate, filtered and concentrated and purified by column chromatography using a heptanes:iPrOAc gradient to afford 100 mg (22%) of methyl 2-(2-methoxypyrimidin-4-yl)acetate as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 5.0 Hz, 1H), 6.96 (d, J = 5.0 Hz, 1H), 4.01 (s, 3H), 3.76 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 165.7, 165.3, 159.4, 114.8, 54.9, 52.4, 43.2. HRMS (ESI) $[M+H]^+$ calc. $C_8H_{11}N_2O_3$: 183.0770, found: 183.0764.

Methyl 2-(5-chloropyrazin-2-yl)acetate (***1q***). To a solution of 2-(5-chloropyrazin-2-yl)acetic acid (509 mg, 3.0 mmol, 1.0 equiv) in DMF (0.5 M) was added potassium carbonate (3.0 equiv) and iodomethane (1.1 equiv). The reaction was stirred at room temperature for 1 h, then quenched with a saturated solution of ammonium chloride and DCM. The organic layer was dried with magnesium sulfate, filtered and concentrated. The crude was purified via flash column chromatography using a heptanes:iPrOAc gradient to afford 290 mg (53%) of methyl 2-(5-chloropyrazin-2-yl)acetate as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.51 (s, 1H), 3.88 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 150.0, 148.7, 143.2, 143.0, 52.7, 40.6. HRMS (ESI) $[M+H]^+$ calc. $C_7H_8ClN_2O_2$: 187.0274, found: 187.0269.

Ethyl 5-(3-bromophenyl)imidazo[5,1-*b*]thiazole-7-carboxylate (***3a***). Ethyl 2-thiazol-2-ylacetate ***1a*** (0.5 mmol) was reacted with 3-bromobenzylamine ***2a*** (2.0 equiv) according to general procedure B. The reaction was performed in acetonitrile on a 0.5 mmol scale to give 68% yield and in DMF on a 0.5 mmol and 6 mmol scale both to give 57% yield. ^{1}H NMR (400 MHz,

DMSO-d_6) δ 8.37 (d, J = 4.2 Hz, 1H), 8.07 – 8.04 (m, 1H), 7.95 – 7.91 (m, 1H), 7.68 – 7.64 (m, 1H), 7.59 (d, J = 4.2 Hz, 1H), 7.52 – 7.46 (m, 1H), 4.32 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.3, 141.1, 136.5, 131.5, 131.2, 130.9, 128.7, 125.0, 122.1, 120.5, 120.2, 119.9, 59.7, 14.2. HRMS (ESI) $[M+H]^+$ calc. $C_{14}H_{12}BrN_2O_2S$: 350.9803, found: 350.9808.

Ethyl 5-(3-iodophenyl)imidazo[5,1-*b*]thiazole-7-carboxylate (***3b***). Ethyl 2-thiazol-2-ylacetate ***1a*** (0.5 mmol) was reacted with 3-iodobenzylamine ***2b*** (2.0 equiv) according to general procedure B to give 133 mg (67%) of a light tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, J = 4.2 Hz, 1H), 8.24 – 8.22 (m, 1H), 7.97 – 7.93 (m, 1H), 7.86 – 7.82 (m, 1H), 7.60 (d, J = 4.2 Hz, 1H), 7.36 – 7.31 (m, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H). 13C NMR (101 MHz, DMSO-d_6) δ 161.5, 141.2, 137.5, 136.5, 134.7, 131.2, 131.0, 125.5, 120.5, 120.5, 120.2, 95.4, 60.0, 14.4. HRMS (ESI) $[M+H]^+$ calc. $C_{14}H_{12}IN_2O_2S$: 398.9664, found 398.9659.

Ethyl 5-(3-hydroxyphenyl)imidazo[5,1-*b*]thiazole-7-carboxylate (***3c***). Ethyl 2-thiazol-2-ylacetate ***1a*** (0.5 mmol) was reacted with 3-hydroxybenzylamine ***2c*** (2.0 equiv) according to general procedure A to give 100 mg (69%) of a light orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.30 (d, J = 4.1 Hz, 1H), 7.58 (d, J = 4.2 Hz, 1H), 7.40 – 7.30 (m, 3H), 6.94 – 6.83 (m, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.6, 157.8, 140.8, 138.3, 130.3, 130.2, 120.3, 120.2, 120.0, 117.0, 116.3, 113.2, 59.9, 14.5. HRMS (ESI) $[M+H]^+$ calc. $C_{14}H_{13}N_2O_3S$ 289.0647, found: 289.0641.

Ethyl 5-(2-methoxyphenyl)imidazo[5,1-*b*]thiazole-7-carboxylate (***3d***). Ethyl 2-thiazol-2-ylacetate ***1a*** (0.46 mmol) was reacted with 2-methoxybenzylamine ***2d*** (2.0 equiv) according to general procedure A to give 102 mg (74%) of a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J = 7.6, 1.8 Hz, 1H), 7.44 (ddd, J = 8.3, 7.5, 1.8 Hz, 1H), 7.38 (d, J = 4.2 Hz, 1H), 7.10 – 7.05 (m, 1H), 7.01 (dd, J = 8.4, 1.0 Hz, 1H), 6.96 (d, J = 4.2 Hz, 1H), 4.45 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 156.7, 139.8, 137.2, 132.2, 131.1, 121.4, 121.2, 120.2, 118.7, 117.1, 111.2, 60.5, 55.6, 14.7. HRMS (ESI) $[M+H]^+$ calc. $C_{15}H_{15}N_2O_3S$: 303.0798, found: 303.0792.

Ethyl 5-(3-(methoxycarbonyl)phenyl)imidazo[5,1-*b*]thiazole-7-carboxylate (***3e***). To a solution of HCl salt of methyl 4-(aminomethyl)benzoate hydrochloride ***2e*** (1.0 mmol, 200 mg) in acetonitrile was added was added Amberlyst 21 (380 mg). The suspension was stirred at room temperature for 30 min, then filtered and washed with CH_2Cl_2 to remove the resin. The filtrant was collected and concentrated in vacuo. The residue was then redissolved in DMF (1 mL) and was reacted with ethyl 2-(thiazol-2-yl)acetate ***1a*** (0.5 mmol, 90 mg) according to general procedure A to give 103 mg (62% yield) of a white solid. 1H NMR (400 MHz, $CDCl_3$) δ 8.49 (t, J = 1.8 Hz, 1H), 8.19 – 8.07 (m, 2H), 7.85 (d, J = 4.2 Hz, 1H), 7.59 (td, J = 7.8, 0.6 Hz, 1H), 7.13 (d, J = 4.2 Hz, 1H), 4.47 (q, J = 7.1 Hz, 2H), 3.96 (s, 3H), 1.45 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz,

$CDCl_3$) δ 166.5, 162.6, 132.1, 131.7, 131.1, 130.3, 130.1, 129.4, 127.4, 119.5, 118.6, 61.0, 52.5, 14.8. HRMS (ESI) $[M+H]^+$ calc. ($C_{16}H_{15}N_2O_4S$): 331.0753, found: 331.0747.

Ethyl 5-(4-cyanophenyl)imidazo[5,1-*b*]thiazole-7-carboxylate (***3f***). Ethyl 2-(thiazol-2-yl)acetate ***1a*** (0.5 mmol, 90 mg) was reacted with 4-(aminomethyl)benzonitrile ***2f*** (1.0 mmol, 130 μL) according to general procedure A to give 116 mg (78% yield) of a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.99 (m, 2H), 7.85 (d, *J* = 4.2 Hz, 1H), 7.79 – 7.77 (m, 2H), 7.19 (d, *J* = 4.2 Hz, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 141.5, 137.0, 133.8, 133.0, 127.1, 122.9, 120.3, 118.4, 112.6, 61.2, 14.7. HRMS (ESI) $[M+H]^+$ calc. ($C_{15}H_{12}N_3O_2S$): 298.0650, found: 298.0645.

Ethyl 5-(4-(methylsulfonyl)phenyl)imidazo[5,1-*b*]thiazole-7-carboxylate (***3g***). To a solution of HCl salt of (4-methylsulfonylphenyl)methanamine ***2g*** (1.0 mmol, 220 mg) in acetonitrile was added was added Amberlyst 21 (380 mg). The suspension was stirred at room temperature for 30 min, then filtered and washed with DCM to remove the resin. The filtrant was collected and concentrated in vacuo. The residue was then redissolved in DMF (1 mL) and was reacted with ethyl 2-(thiazol-2-yl)acetate ***1a*** (0.5 mmol, 90 mg) according to general procedure A to give 140 mg (80% yield) of a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.05 (m, 4H), 7.87 (d, *J* = 4.2 Hz, 1H), 7.20 (d, *J* = 4.2 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.11 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H).13C NMR (101 MHz, $CDCl_3$) δ 162.2, 141.4, 140.6, 136.8, 134.6, 128.2, 127.3, 122.8, 120.2, 118.3, 61.0, 44.5, 14.6. HRMS (ESI) $[M+H]^+$ calc. ($C_{15}H_{15}N_2O_4S_2$): 351.0473, found: 351.0468.

Ethyl 5-(pyridin-2-yl)imidazo[5,1-*b*]thiazole-7-carboxylate (***3h***). Ethyl 2-thiazol-2-ylacetate ***1a*** (0.5 mmol) was reacted with 4-pyridylmethanamine ***2h*** (1.1 equiv) according to general procedure A to give 45 mg (30%) of a red solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (d, *J* = 4.2 Hz, 1H), 8.71 – 8.68 (m, 1H), 8.17 – 8.14 (m, 1H), 8.00 – 7.95 (m, 1H), 7.63 (d, *J* = 4.0 Hz, 1H), 7.47 – 7.43 (m, 1H), 4.33 (q, J = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.4, 149.1, 148.1, 141.6, 137.5, 136.7, 123.4, 122.1, 120.5, 120.3, 120.2, 60.0, 14.4. HRMS (ESI) $[M+H]^+$ calc. $C_{13}H_{12}N_3O_2S$ 274.0650, found: 274.0645.

Ethyl 5-(pyridin-4-yl)imidazo[5,1-*b*]thiazole-7-carboxylate (***3i***). Ethyl 2-thiazol-2-ylacetate ***1a*** (0.5 mmol) was reacted with 4-pyridylmethanamine ***2i*** (2.0 equiv) according to general procedure A to give 56 mg (41%) of a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 – 8.70 (m, 2H), 8.57 (d, *J* = 4.1 Hz, 1H), 7.94 – 7.91 (m, 2H), 7.69 (d, *J* = 4.2 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.4, 150.4, 142.1, 135.9, 135.7, 121.1, 121.0, 120.6, 120.0, 60.0, 14.4. HRMS (ESI) $[M+H]^+$ calc. $C_{13}H_{12}N_3O_2S$ 274.0650, found: 274.0645.

Ethyl 5-(thiazol-2-yl)imidazo[5,1-*b*]thiazole-7-carboxylate (***3j***). Ethyl 2-(thiazol-2-yl)acetate ***1a*** (0.5 mmol, 90 mg) was reacted with thiazol-2-ylmethanamine ***2j*** (1.0 mmol, 110 mg) according to general procedure A to give 77 mg (55% yield) of

a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 4.2 Hz, 1H), 7.86 (d, *J* = 3.2 Hz, 1H), 7.39 (d, *J* = 3.2 Hz, 1H), 7.13 (d, *J* = 4.2 Hz, 1H), 4.66 (s, 2H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 157.9, 143.4, 141.1, 133.5, 122.1, 121.4, 119.9, 119.0, 61.1, 14.7. HRMS (ESI) $[M+H]^+$ calc. ($C_{11}H_{10}N_3O_2S_2$): 280.0214, found: 280.0209.

Ethyl 5-(1-methyl-1H-pyrazol-4-yl)imidazo[5,1-*b*]thiazole-7-carboxylate (***3k***). Ethyl 2-(thiazol-2-yl)acetate ***1a*** (0.5 mmol) was reacted with (1-methylpyrazol-4-yl)methanamine ***2k*** (2.0 equiv) according to general procedure A but instead of room temperature was heated to 80 °C for 18 h to give 83 mg (60% yield) of an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.89 (s, 1H), 7.63 (d, *J* = 4.2 Hz, 1H), 7.08 (d, *J* = 4.2 Hz, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 3.98 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 139.2, 136.7, 133.2, 129.2, 121.1, 119.1, 117.8, 112.5, 60.8, 39.4, 14.7. HRMS (ESI) $[M+H]^+$ calc. ($C_{12}H_{13}N_4O_2S$): 277.0759, found: 277.0754.

Ethyl 5-cyclopropylimidazo[5,1-*b*]thiazole-7-carboxylate (***3l***). Ethyl 2-(thiazol-2-yl)acetate ***1a*** (1.5 mmol) was reacted with cyclopropylamine ***2l*** (2.0 equiv) according to general procedure A but instead of room temperature was heated to 80 °C for 18 h to give 110 mg of an inseparable mixture of product and succinimide (31% yield, adjusted to 26% based on NMR) of a red-orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ *8.41 (bs, 1H), 7.51 (d, *J* = 4.2 Hz, 1H), 6.99 (d, *J* = 4.2 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), *2.76 (s, 2H), 2.01 (tt, *J* = 8.3, 5.0 Hz, 1H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.20 – 1.05 (m, 2H), 1.08 – 0.90 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ *177.3, 162.6, 141.4, 138.6, 119.9, 118.2, 117.0, 60.6, *29.7, 14.8, 8.1, 7.0. HRMS (ESI) $[M+H]^+$ calc. ($C_{11}H_{13}N_2O_2S$): 237.0698, found: 237.0691.

Ethyl 5-vinylimidazo[5,1-*b*]thiazole-7-carboxylate (***3m***). Ethyl 2-(thiazol-2-yl)acetate ***1a*** (1.5 mmol) was reacted with allylamine ***2m*** (2.0 equiv) according to general procedure A to give 140 mg (42% yield) of an orange amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 4.2 Hz, 1H), 7.09 (d, *J* = 4.1 Hz, 1H), 6.80 (dd, *J* = 17.7, 11.6 Hz, 1H), 6.10 (d, *J* = 17.8 Hz, 1H), 5.55 (d, *J* = 11.6 Hz, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 139.9, 137.5, 123.9, 121.6, 119.2, 118.0, 117.9, 60.9, 14.7. HRMS (ESI) $[M+H]^+$ calc. ($C_{10}H_{11}N_2O_2S$): 223.0541, found: 223.0533.

tert-butyl 5-(3-bromophenyl)-3-methylimidazo[5,1-*b*]thiazole-7-carboxylate (***4b***). *tert*-butyl 2-(4-methylthiazol-2-yl)acetate ***1b*** (0.5 mmol) was reacted with 3-bromobenzylamine ***2a*** (2.0 equiv) according to general procedure A to give 160 mg (81%) of an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 – 7.84 (m, 1H), 7.74 – 7.70 (m, 1H), 7.66 – 7.62 (m, 1H), 7.48 – 7.43 (m, 1H), 7.08 – 7.06 (m, 1H), 2.08 (d, *J* = 1.2 Hz, 3H), 1.55 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.7, 140.6, 137.3, 132.5, 132.2, 132.0, 129.8, 129.3, 129.1, 120.8, 114.1, 79.9, 28.0, 14.3. HRMS (ESI) $[M+H]^+$ calc. $C_{17}H_{18}BrN_2O_2S$ 393.0272, found: 393.0267.

Ethyl 5-(3-bromophenyl)-3-(trifluoromethyl)imidazo[5,1-*b*]thiazole-7-carboxylate (***4c***). Ethyl 2-[4-(trifluoromethyl)thiazol-2-yl]acetate ***1c*** (0.5 mmol, 120 mg) was reacted with 3-bromobenzylamine ***2a*** (1.0 mmol, 130 μL) according to general procedure A to give 145 mg (69% yield) of a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (brs, 1H), 7.63 (dd, *J* = 8.1, 3.1 Hz, 1H), 7.60 – 7.58 (m, 1H), 7.48 – 7.45 (m, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H), ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 140.2, 138.7, 133.5, 133.4, 131.6, 129.6, 129.0 (q, *J* = 1.8 Hz), 124.6 (q, *J* = 4.9 Hz), 122.8, 122.6, 122.1, 118.6 (q, *J* = 270.4 Hz), 61.3, 14.7. HRMS (ESI) $[M+H]^+$ calc. ($C_{15}H_{11}BrF_3N_2O_2S$): 418.9677, found: 418.9673.

Methyl 2-bromo-5-(3-bromophenyl)imidazo[5,1-*b*]thiazole-7-carboxylate (***4d***). Methyl 2-(5-bromo-1,3-thiazol-2-yl)acetate ***1d*** (0.5 mmol) was reacted with 3-bromobenzylamine ***2a*** (2.0 equiv) according to general procedure B to give 106 mg (51%) of an orange solid ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 – 8.82 (m, 1H), 8.06 – 8.05 (m, 1H), 7.96 – 7.92 (m, 1H), 7.70 – 7.67 (m, 1H), 7.51 – 7.46 (m, 1H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.6, 139.1, 137.5, 132.0, 131.1, 130.8, 129.0, 125.6, 122.3, 122.1, 120.8, 107.2, 51.6. HRMS (ESI) $[M+H]^+$ calc. $C_{13}H_9Br_2N_2O_2S$ 414.8751, found: 414.8743.

Ethyl 5-(3-bromophenyl)-2-((*tert*-butoxycarbonyl)amino)imidazo[5,1-*b*][1,3,4]thiadiazole-7-carboxylate (***4e***). Ethyl 2-[5-(*tert*-butoxycarbonylamino)-1,3,4-thiadiazol-2-yl]acetate ***1e*** (0.5 mmol) was reacted with 3-bromobenzylamine ***2a*** (2.0 equiv) according to general procedure B to give 210 mg (90%) of a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 8.43 – 8.37 (m, 1H), 8.23 – 8.16 (m, 1H), 7.67 – 7.60 (m, 1H), 7.54 – 7.45 (m, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.53 (s, 9H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.9, 160.7, 152.8, 135.1, 134.5, 131.6, 130.9, 130.4, 127.9, 124.6, 122.0, 118.5, 83.2, 60.2, 27.7, 14.4. HRMS (ESI) $[M+H]^+$ calc. $C_{18}H_{20}BrN_4O_4S$ 467.0389, found: 467.0383.

Ethyl 2-amino-5-(3-bromophenyl)imidazo[5,1-*b*][1,3,4]thiadiazole-7-carboxylate (***4f***). Ethyl 2-(5-amino-1,3,4-thiadiazol-2-yl)acetate ***1f*** (0.5 mmol) was reacted with 3-bromobenzylamine ***2a*** (2.0 equiv) according to general procedure A to give 150 mg (82%) of a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 – 8.40 (m, 1H), 8.23 – 8.19 (m, 1H), 8.01 (s, 2H), 7.64 – 7.59 (m, 1H), 7.51 – 7.45 (m, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.0, 161.2, 135.1, 133.3, 131.3, 130.9, 130.8, 127.8, 124.5, 122.0, 119.0, 60.1, 14.4. HRMS (ESI) $[M+H]^+$ calc. $C_{13}H_{12}BrN_4O_2S$ 366.9864, found: 366.9846.

2-amino-5-(3-bromophenyl)-N,N-dimethylimidazo[5,1-*b*][1,3,4]thiadiazole-7-carboxamide (***4g***). 2-(5-amino-1,3,4-thiadiazol-2-yl)-*N,N*-dimethylacetamide ***1g*** was reacted with 3-bromobenzylamine ***2a*** (2.0 equiv) according to general procedure A but instead of room temperature was heated to 80 °C for 18 h to give 60 mg (33%) of a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.40 (t, *J* = 1.9 Hz, 1H), 8.20 (dt, *J* = 1.4, 7.9 Hz, 1H), 7.76 (s, 2H), 7.56 (dt, *J* = 1.5, 8.1 Hz, 1H), 7.45 (t,

J = 7.9 Hz, 1H), 3.18 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.8, 161.0, 133.1, 132.8, 131.3, 131.0, 130.9, 127.5, 124.5, 124.3, 122.1, 37.6, 36.1. HRMS (ESI) $[M+H]^+$ calc. $C_{13}H_{13}BrN_5OS$ 366.0024, found: 366.0019.

5-(3-bromophenyl)-*N*-methoxy-*N*-methylimidazo[5,1-*b*]thiazole-7-carboxamide (***4h***). *N*-methoxy-*N*-methyl-2-thiazol-2-yl-acetamide ***1h*** (80 mg, 0.43 mmol) was reacted with 3-bromobenzylamine ***2a*** (2.0 equiv) according to general procedure A but instead of room temperature was heated to 80 °C for 18 h to afford 85 mg (54%) of an off-white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.98 (m, 1H), 7.80 (d, *J* = 4.3 Hz, 1H), 7.78 – 7.74 (m, 1H), 7.57 – 7.52 (m, 1H), 7.40 – 7.33 (m, 1H), 7.10 (d, *J* = 4.2 Hz, 1H), 3.91 (s, 3H), 3.62 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 141.2, 136.3, 132.1, 132.0, 130.6, 129.7, 125.1, 124.2, 123.3, 120.0, 118.0, 61.9, 35.1. HRMS (ESI) $[M+H]^+$ calc. $C_{14}H_{13}BrN_3O_2S$ 365.9912, found: 365.9908.

Ethyl 5-(3-bromophenyl)-1-methyl-1*H*-imidazo[1,5-*a*]imidazole-7-carboxylate (***4i***). Methyl 2-(1-methylimidazol-2-yl)acetate hydrochloride ***1i*** (0.45 mmol) was reacted with 3-bromobenzylamine ***2a*** (2.0 equiv) according to general procedure A to give 54 mg (34%) of an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 – 8.01 (m, 2H), 7.91 – 7.87 (m, 1H), 7.56 – 7.52 (m, 1H), 7.50 (d, *J* = 2.3 Hz, 1H), 7.47 – 7.41 (m, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.99 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.9, 142.4, 132.0, 131.1, 130.1, 127.8, 127.2, 126.9, 123.1, 122.3, 106.4, 104.6, 59.0, 35.1, 14.5. HRMS (ESI) $[M+H]^+$ calc. $C_{15}H_{15}BrN_3O_2$ 348.0348, found: 348.0342.

Ethyl 5-(3-bromophenyl)-1*H*-imidazo[5,1-*c*][1,2,4]triazole-7-carboxylate (***4j***). Ethyl 2-(4*H*-1,2,4-triazol-3-yl)acetate ***1j*** (0.5 mmol) was reacted with 3-bromobenzylamine ***2a*** (1.1 equiv) according to general procedure A to give 67 mg (40%) of a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 1H), 8.41 – 8.35 (m, 1H), 8.25 – 8.17 (m, 1H), 7.59 – 7.52 (m, 1H), 7.52 – 7.43 (m, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.4, 147.3, 131.3, 131.1, 130.3, 127.2, 126.6, 123.2, 122.1, 102.7, 59.1, 14.6. HRMS (ESI) $[M+H]^+$ calc. $C_{13}H_{12}BrN_4O_2$ 335.0144, found: 335.0138.

Ethyl 5-(3-bromophenyl)imidazo[5,1-*b*]benzo[*d*]thiazole-7-carboxylate (***4k***). Methyl 2-(benzo[*d*]thiazol-2-yl)acetate ***1k*** (0.5 mmol) was reacted with 3-bromobenzylamine ***2a*** (2.0 equiv) according to general procedure B to give 130 mg (65%) of a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 – 8.04 (m, 1H), 8.00 – 7.97 (m, 1H), 7.85 – 7.79 (m, 2H), 7.62 – 7.56 (m, 1H), 7.51 – 7.41 (m, 2H), 7.39 – 7.35 (m, 1H), 4.34 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H).^{13}C NMR (101 MHz, DMSO-d_6) δ 161.4, 139.3, 138.5, 133.0, 132.7, 132.0, 131.7, 131.5, 130.7, 128.1, 126.3, 126.1, 121.7, 121.2, 114.1, 59.9, 14.2. HRMS (ESI) $[M+H]^+$ calc. $C_{18}H_{14}BrN_2O_2S$ 400.9959, found: 400.9960.

Ethyl 5-(3-bromophenyl)-1-methyl-1*H*-benzo[*d*]imidazole[1,5-*a*]imidazole-7-carboxylate (***4l***). Ethyl 2-(1-methylbenzimidazol-2-yl)acetate ***1l*** was reacted with 3-bromobenzylamine ***2a*** (2.0 equiv) according to general procedure A

to give 108 mg (54%) of a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 – 7.97 (m, 1H), 7.88 – 7.84 (m, 1H), 7.74 – 7.71 (m, 1H), 7.65 – 7.60 (m, 2H), 7.59 – 7.54 (m, 1H), 7.52 – 7.47 (m, 1H), 7.28 – 7.23 (m, 1H), 4.31 (q, J = 7.1 Hz, 2H), 4.12 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.1, 144.3, 139.0, 132.2, 131.6, 131.0, 130.8, 130.1, 126.3, 125.3, 123.1, 121.8, 120.6, 112.1, 110.9, 104.9, 59.1, 31.4, 14.3. HRMS (ESI) $[M+H]^+$ calc. $C_{19}H_{17}BrN_3O_2$ 398.0504, found: 398.0499

Methyl 1-(3-bromophenyl)benzo[*d*]imidazo[5,1-*b*]oxazole-3-carboxylate (***4m***). Methyl 2-(benzo[*d*]oxazol-2-yl)acetate ***1m*** (1.5 mmol) was reacted with 3-bromobenzylamine ***2a*** (2.0 equiv) according to general procedure A to give 75 mg (13%) of a white solid following reverse phase HPLC purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 – 8.02 (m, 1H), 7.94 – 7.88 (m, 2H), 7.81 – 7.75 (m, 1H), 7.75 – 7.70 (m, 1H), 7.63 – 7.53 (m, 2H), 7.51 – 7.45 (m, 1H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.1, 153.7, 152.5, 132.4, 131.9, 131.4, 131.3, 130.0, 126.7, 126.3, 126.3, 125.0, 124.8, 122.2, 113.4, 113.3, 104.8, 51.2. HRMS (ESI) $[M+H]^+$ calc. $C_{17}H_{12}BrN_2O_3$ 371.0031, found: 371.0026.

Methyl 6-(3-bromophenyl)imidazo[1,5-*a*]pyrimidine-8-carboxylate (***4n***). Methyl 2-(2-pyrimidyl)acetate ***1n*** (0.5 mmol) was reacted with 3-bromobenzylamine ***2a*** (2.0 equiv) according to general procedure A to give 70 mg (42%) of a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (dd, J = 7.3, 1.8 Hz, 1H), 8.65 – 8.59 (m, 1H), 8.07 – 8.01 (m, 1H), 7.95 – 7.84 (m, 1H), 7.78 – 7.70 (m, 1H), 7.59 – 7.50 (m, 1H), 7.07 (dd, J = 7.3, 3.8 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.0, 151.4, 140.8, 134.0, 132.1, 131.5, 130.9, 130.6, 130.5, 126.9, 122.0, 119.1, 110.3, 50.8. HRMS (ESI) $[M+H]^+$ calc. $C_{14}H_{11}BrN_3O_2$: 332.0035, found: 332.0029.

Methyl 3-(3-bromophenyl)imidazo[1,5-*a*]pyrazine-1-carboxylate (***4o***). Methyl 2-pyrazineacetate ***1o*** (0.5 mmol) was reacted with 3-bromobenzylamine ***2a*** (1.1 equiv) according to general procedure B to give 120 mg (72%) of a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (d, J = 1.7 Hz, 1H), 8.59 (dd, J = 5.0, 1.6 Hz, 1H), 8.07 – 8.05 (m, 1H), 7.95 – 7.91 (m, 1H), 7.90 (d, J = 5.0 Hz, 1H), 7.81 – 7.77 (m, 1H), 7.60 – 7.55 (m, 1H), 3.95 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.1, 146.0, 138.0, 132.7, 131.2, 130.9, 130.6, 130.2, 128.7, 127.3, 124.5, 122.2, 116.3, 51.7. HRMS (ESI) $[M+H]^+$ calc. $C_{14}H_{11}BrN_3O_2$: 332.0035, found: 332.0030.

Methyl 3-(3-bromophenyl)-5-methoxyimidazo[1,5-*c*]pyrimidine-1-carboxylate (***4p***). Methyl 2-(2-methoxypyrimidin-4-yl)acetate ***1p*** (0.27 mmol) was reacted with 3-bromobenzylamine ***2a*** (2.0 equiv) according to general procedure A to give 80 mg (81%) of a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 – 7.90 (m, 1H), 7.74 – 7.68 (m, 2H), 7.65 (d, J = 6.4 Hz, 1H), 7.60 (d, J = 6.4 Hz, 1H), 7.47 – 7.40 (m, 1H), 3.96 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.7, 147.8, 138.5, 137.6, 137.2, 133.3, 133.1, 131.6, 129.5, 129.3, 120.9, 120.3, 106.5, 55.6, 51.3. HRMS (ESI) $[M+H]^+$ calc. $C_{15}H_{13}BrN_3O_3$ 362.0140, found: 362.0135.

Methyl 3-(3-bromophenyl)-6-chloroimidazo[1,5-a]pyrazine-1-carboxylate (***4q***). Methyl 2-(5-chloropyrazin-2-yl)acetate ***1q*** (0.5 mmol) was reacted with 3-bromobenzylamine ***2a*** (1.1 equiv) according to general procedure B to give 120 mg (65%) of a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.02 (s, 1H), 7.91 – 7.89 (m, 1H), 7.80 – 7.76 (m, 1H), 7.71 – 7.67 (m, 1H), 7.50 – 7.45 (m, 1H), 3.95 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 161.8, 144.5, 139.0, 133.7, 132.7, 132.6, 130.8, 130.3, 130.0, 129.4, 124.6, 121.8, 120.4, 51.9. HRMS (ESI) $[M+H]^+$ calc. $C_{14}H_{10}BrClN_3O_2$ 365.9645, found: 365.9639.

1-(*tert*-butyl) 7-methyl 9-(3-bromophenyl)-3,4-dihydroimidazo[1,5-*a*][1,8]naphthyridine-1,7(2*H*)-dicarboxylate (***4r***). (8-Boc-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl)-acetic acid methyl ester ***1r*** (0.5 mmol) was reacted with 3-bromobenzylamine ***2a*** (2.0 equiv) according to general procedure B to give 170 mg (70%) of a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, J = 9.0 Hz, 1H), 7.72 (s, 1H), 7.61 – 7.53 (m, 2H), 7.38 – 7.31 (m, 1H), 7.19 (d, J = 9.1 Hz, 1H), 4.16 – 4.05 (m, 1H), 3.87 (s, 3H), 3.49 – 3.36 (m, 1H), 2.93 – 2.84 (m, 1H), 2.81 – 2.70 (m, 1H), 2.06 – 1.85 (m, 2H), 1.02 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.6, 152.2, 138.5, 136.7, 133.8, 132.8, 132.1, 131.2, 129.2, 128.2, 121.0, 120.6, 118.7, 115.8, 81.8, 51.3, 45.0, 27.8, 24.9, 23.0. HRMS (ESI) $[M+H]^+$ calc. $C_{23}H_{25}BrN_3O_4$ 486.1028, found: 486.1010.

Methyl 7-(3-bromophenyl)imidazo[1,5-*b*]pyridazine-5-carboxylate (***4t***). Methyl pyridazin-3-yl-acetate ***1t*** (0.5 mmol) was reacted with 3-bromobenzylamine ***2a*** (2.0 equiv) according to general procedure B to give 130 mg (78%) of a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (d, J = 4.2 Hz, 1H), 8.61 – 8.50 (m, 2H), 8.41 (d, J = 7.9 Hz, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.27 (dd, J = 9.3, 4.4 Hz, 1H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.3, 146.5, 137.9, 131.9, 130.8, 130.6, 129.9, 129.7, 128.0, 126.4, 121.7, 120.8, 117.7, 51.5. HRMS (ESI) $[M+H]^+$ calc. $C_{14}H_{11}BrN_3O_2$: 332.0035, found: 332.0029. Intermediate ***4t*** was previously synthesized and claimed in a patent (reference 1d) but no characterization data was reported.

Ethyl 2-(((1-methyl-1*H*-pyrazol-4-yl)methyl)imino)-2-(thiazol-2-yl)acetate ***(5)***. Ethyl 2-(thiazol-2-yl)acetate ***1a*** (0.5 mmol, 90 mg) was reacted with (1-methylpyrazol-4-yl)methanamine ***2k*** (2.0 equiv, 110 mg) according to general procedure A to give 70 mg (51% yield) of a white solid (*E/Z* geometry was not determined). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 3.2 Hz, 1H), 7.48 (s, 1H), 7.44 (d, J = 3.2 Hz, 1H), 7.37 (s, 1H), 4.66 (s, 2H), 4.51 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 163.4, 155.6, 144.3, 138.7, 129.3, 122.4, 117.9, 62.3, 49.2, 39.0, 14.3. HRMS (ESI) $[M+H]^+$ calc. ($C_{12}H_{15}N_4O_2S$): 279.0916, found: 279.0919.

2-(5-amino-1,3,4-thiadiazol-2-yl)-2-((3-bromobenzyl)amino)-N,N-dimethylacetamide (***6***). 2-(5-amino-1,3,4-thiadiazol-2-yl)-*N,N*-dimethylacetamide ***1g*** (0.5 mmol) was reacted with 3-bromobenzylamine ***2a*** (2.0 equiv) according to general procedure A to give 80 mg (43%) of an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 – 7.52 (m, 1H), 7.46 – 7.41 (m,

1H), 7.34 – 7.24 (m, 2H), 7.11 (s, 2H), 4.88 (d, J = 9.1 Hz, 1H), 3.70 – 3.64 (m, 2H), 3.21 – 3.11 (m, 1H), 2.98 (s, 3H), 2.85 (s, 3H).^{13}C NMR (101 MHz, DMSO-d_6) δ 169.2, 169.0, 159.1, 143.0, 130.6, 130.3, 129.6, 127.0, 121.6, 57.0, 50.0, 36.5, 35.4. HRMS (ESI) $[M+H]^+$ calc. $C_{13}H_{17}BrN_5OS$ 370.0337, found 370.0334.

(1-(3-Bromophenyl)-4-methyl-4*H*-benzo[*d*]imidazo[1,5-*a*]imidazol-3-yl)(phenyl)methanone (***4u***) and 2-(3-bromophenyl)-4-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)-5-phenyloxazole (***7***). 2-(1-Methylbenzimidazol-2-yl)-1-phenyl-ethanone ***1u*** (0.46 mmol) was reacted with 3-bromobenzylamine ***2a*** (2.0 equiv) according to general procedure A, followed by trituration from a mixture of MeOH/DCM for the ketone product, to give ***4u***, 43 mg (22%) of a yellow solid, and ***7***, 88 mg (44%) of a white solid.

Data for (***4u***):

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.28 – 8.23 (m, 2H), 8.05 (t, J = 1.9 Hz, 1H), 7.93 (dt, J = 1.3, 7.8 Hz, 1H), 7.77 (ddd, J = 0.9, 2.1, 7.9 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.62 – 7.50 (m, 5H), 7.34 (ddd, J = 1.1, 7.4, 8.4 Hz, 1H), 4.33 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 184.0, 146.0, 139.0, 138.8, 132.1, 132.0, 131.1, 131.0, 131.0, 130.3, 130.0, 127.7, 126.8, 125.6, 123.1, 122.0, 121.4, 115.5, 112.4, 111.6, 32.2. HRMS (ESI) $[M+H]^+$ calc. $C_{23}H_{17}ON_3Br$: 430.0550, found: 430.0541.

Data for (***7***):

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.36 (t, J = 1.9 Hz, 1H), 8.21 (dt, J = 1.3, 7.8 Hz, 1H), 8.19 – 8.15 (m, 2H), 7.90 – 7.80 (m, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.60 (t, J = 7.9 Hz, 1H), 7.53 – 7.44 (m, 3H), 7.38 (ddd, J = 1.2, 7.1, 8.2 Hz, 1H), 7.34 – 7.26 (m, 1H), 3.98 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.3, 150.8, 145.5, 142.6, 136.4, 134.4, 132.0, 130.3, 129.3, 129.2, 128.7, 127.8, 127.3, 127.0, 125.9, 123.6, 122.9, 122.8, 119.9, 111.1, 31.9. HRMS (ESI) $[M+H]^+$ calc. $C_{23}H_{17}ON_3Br$: 430.0550, found: 430.0547.

13-((3-bromobenzyl)amino)benzo[4,5]thiazolo[3,2-*a*]benzo[4,5]thiazolo[3,2-*d*]pyrazine-6-carbonitrile (***8***). 2-(1,3-benzothiazol-2-yl)acetonitrile ***1v*** (0.5 mmol) was reacted with 3-bromobenzylamine ***2a*** (1.1 equiv) according to general procedure B to give 100 mg of a yellow solid containing ***8*** and an inseparable unknown by-product in a 6.7:1 molar ratio for a 40% combined yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.53 (t, J = 6.4 Hz, 1H), 8.32 (dd, J = 8.0, 1.3 Hz, 1H), 8.26 – 8.22 (m, 1H), 8.12 (dd, J = 8.2, 1.2 Hz, 1H), 7.95 (dd, J = 8.0, 0.9 Hz, 1H), 7.69 (td, J = 8.1, 7.7, 1.4 Hz, 1H), 7.64 (ddd, J = 8.6, 7.2, 1.3 Hz, 1H), 7.56 (ddd, J = 8.3, 7.4, 1.4 Hz, 1H), 7.51 – 7.46 (m, 2H), 7.46 – 7.41 (m, 1H), 7.34 – 7.28 (m, 2H), 4.66 (d, J = 6.4 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.9, 157.2, 155.5, 152.6, 152.1, 140.3, 135.6, 131.9, 130.8, 130.4, 130.0, 127.3, 127.1, 126.8, 126.2, 125.0, 124.1, 123.0, 122.2, 121.8, 121.3, 118.7, 77.3, 48.1. HRMS (ESI) $[M+H]^+$ calc. $C_{24}H_{16}BrN_4S_2$ 503.0000, found: 502.9994.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Typical experimental procedure and characterization for all products. (PDF)

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Notes

The authors declare no competing financial interest

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[10] With methyl 2-(pyrazin-2-yl)acetate as a test substrate purity enhancements were seen by LCMS when the order of addition was changed from adding solvent last to all reagents, to adding catalyst /oxidant last to heteroaromatic substrate/amine/DMA.

[11] In cases where isolation and purification by trituration was not possible, compounds were isolated by silica gel column chromatography.

[12] No formation of aryl iodide was observed during reaction monitoring by LCMS.

[13] A previous report (ref 8) hypothesized that steric hinderance was why 2-methoxybenzylamine did not work in the reaction.

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[21] Imidazo[1,5-*a*]pyridines and one imidazo[1,5-*a*]pyrimidine could be accessed with prior one-pot methods (ref 5,6,7,8).

[22] Compounds ***5*** and ***6*** were also resubjected to the reaction conditions (heated to 80 °C from the beginning since ***3k*** and ***4g*** are not formed at room temp) following isolation, to afford clean conversion to products ***3k*** and ***4g***.

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[24] Complex fragmentation patterns suggesting possible dimers were observed by LCMS for reactions involving heteroaromatic substrates (***1i***, ***1j***, ***1n***, ***1o***, ***1q*** and ***1v***). We isolated a dimer in one case (example ***8***) as ***4v*** was not seen and ***8*** was the

major by-product. In other cases where the product was one of the major peaks by LCMS (***4i***, ***4j***, ***4n***, ***4o*** and ***4q***), we attribute reduced yields to these dimers. The reduction of amine equivalents from 2 to 1.1 worked well to reduce dimer formation for isolation of ***4j***, ***4o*** and ***4q*** but did not appear to make a difference for ***4i*** and ***4n***. All attempts to isolate and characterize any other putative dimers observed by LCMS *via* silica gel chromatography were unsuccessful.