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PAPER

A one-pot regioselective synthesis of benzo[*d*]imidazo[2,1-*b*]thiazoles†

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Benzo[*d*]imidazo[2,1-*b*]thiazole analogues were synthesized *via* a one-pot metal-free procedure. A series of benzene and pyridine substrates were employed to the methodology. The desired products were generated in moderate to good yields. The effect of substituent group had also been studied.

Introduction

Benzo[*d*]imidazo[2,1-*b*]thiazole derivatives are frequently encountered in bioactive molecules and pharmaceutical chemistry. A wide range of compounds possessing benzo[*d*]imidazo-[2,1-*b*]thiazole scaffold have been employed as antimicrobial agents **A**,[1] antitumor agents **B**,[2] antiallergic agents,[3] and antibacterial agents.[4] Furthermore, labeled molecules (Fig. 1, **C**) with this core skeleton have promised utilization for PET imaging of Alzheimer's patients brains as well as β-amyloid plaques.[5] In addition, investment on the biological activity of benzo[*d*]-imidazo[2,1-*b*]thiazole derivatives also revealed its potential role as particular kinase inhibitors and receptors (Fig. 1, **D**).[6]

As a class of privileged substructures, the development of the core scaffold has attracted enormous attention. Benzo[*d*]thiazol-2-amine and 2-bromo-1-phenylethanone derivatives could undergo nucleophilic substitution and nucleophilic addition to generate the desired product. Wu and co-workers reported a copper-catalyzed coupling reaction of 2-iodobenzothiazole with 2-iodoaniline procedure.[7] Bakherad developed a method based on a Sonogashira coupling tandem reaction with aryl iodide and 3-(prop-2-yn-1-yl)benzo[*d*]thiazol-2(3*h*)-imine to afford the target molecule.[8] In addition, the microwave promoted Ugi-type multicomponent reaction of heterocyclic amidines with aldehydes and isocyanides approach has been deeply studied.[9] Recent achievement on flow chemistry methods and aqueous phase synthesis provided intriguing access to benzo[*d*]imidazo-[2,1-*b*]thiazole.[10] A [4 + 2] type reaction procedure emerged as a facile way to construct triheterocyclic compounds.[11] Despite the previous accomplishments to obtain the skeleton, an economical route still may be required for the synthesis of benzo[*d*]imidazo-[2,1-*b*]thiazole derivatives.

Our primary synthetic interests focus on transition-metal free construction of fused heterocycle compounds.[12]

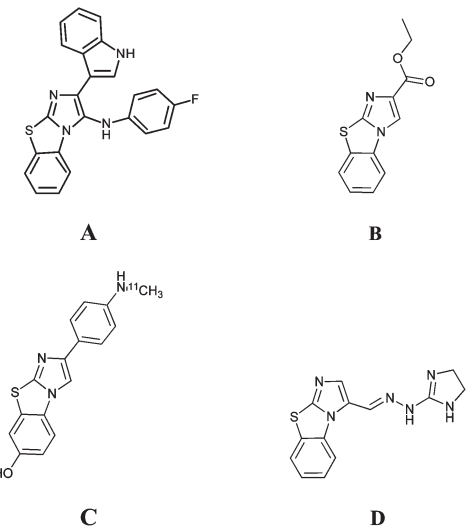
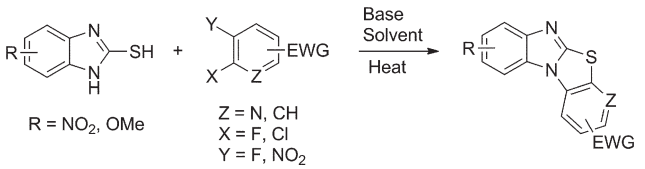


Fig. 1 Examples of benzo[*d*]imidazo[2,1-*b*]thiazole with biological activity.



Scheme 1 Proposed procedure for the synthesis of benzo[*d*]imidazo-[2,1-*b*]thiazole.

Binucleophiles[13] were frequently employed in our previous research due to their diversity and high chemical selectivity. Herein, we report a facile one-pot approach based on an SNAr reaction starting from binucleophile substrates to obtain benzo[*d*]-imidazo[2,1-*b*]thiazole derivatives (Scheme 1).

Result and discussion

We initially optimized the reaction conditions, including solvent, base and temperature with 2-mercaptobenzimidazole and

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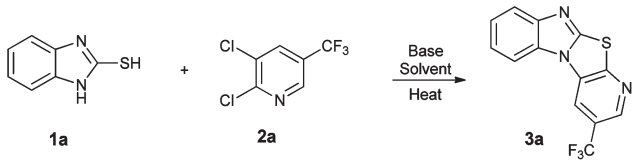
Table 1 Optimization of reaction conditions[a]



Entry	Base	Solvent	*T*/°C	Yield[c] (%)
1	K_2CO_3	DMF	80	n.d[b]
2	K_2CO_3	DMF	100	Trace
3	K_2CO_3	DMF	130	43[c]
4	Cs_2CO_3	DMF	130	53
5	K_3PO_4	DMF	130	41
6	NaOH	DMF	130	n.d
7	**Cs_2CO_3**	**DMSO**	**130**	**64**
8	K_2CO_3	DMSO	130	47

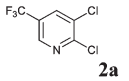
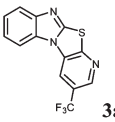
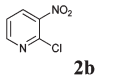
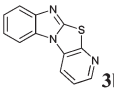
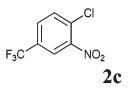
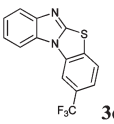
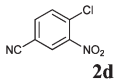
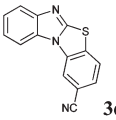
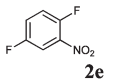
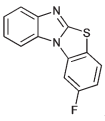
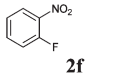
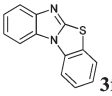
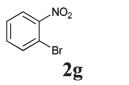
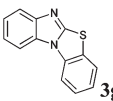
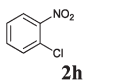
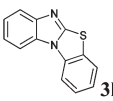
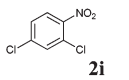
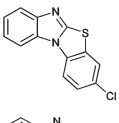
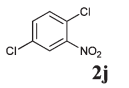
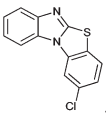
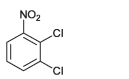
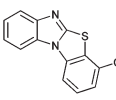
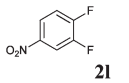
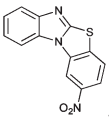
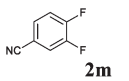
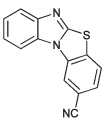
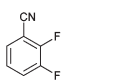
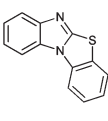
[a] The reaction of **1a** with **2a** was conducted under a nitrogen atmosphere for 6 hours. [b] Not detected. [c] Isolated yields.

2,3-dichloro-5-(trifluoromethyl) pyridine. The results are presented in Table 1. The yields increased as the temperature rose (entries 1–3). Several bases were selected and Cs_2CO_3 was relatively efficient compared to K_2CO_3 and K_3PO_4. No desired product was detected when NaOH was employed as the base. DMSO was more suitable due to its stability at high temperatures and remarkable solubility. The optimal reaction conditions are listed in entry 7. The yields of the expected product could be up to 64%.

With the optimized conditions in hand, we then examined the scope of this methodology. Substrates of benzene and pyridine with double leaving groups at the *ortho*-position were employed in the process (Table 2). To our delight, the desired products were generated in moderate to good yields. The result exhibited the feasibility to construct benzo[*d*]imidazo[2,1-*b*]thiazole and imidazo[2′,1′ : 2,3]thiazolo[5,4-*b*]pyridine derivatives. Products **3a** and **3b** revealed its tolerance to pyridine substrates. Benzene substrates with halogen and nitro groups were more efficient than those with double halogen groups at the *ortho*-position (**2i**–**2n**). This phenomenon could probably be due to the inferior chemical selectivity at high temperatures for substrates **2i**, **2m**, **2n**. Besides, the conjugative effect makes the sulfur atom more reactive than the nitrogen atom and the nitro group adjacent to the halogen makes it easier to be substituted. Substrate **3f**, **3g**, **3h** shared the same product and the isolated yields had an obvious difference. The C–F bond was relatively stable compared to the C–Br and C–Cl bonds. The structure of compound **2a** was confirmed by X-ray diffraction analysis (Fig. 2).†

As we proposed, the methodology possibly followed the SNAr mechanism and therefore the substituent group might have a strong impact on the reaction. To verify this hypothesis, we employed 6-methoxy-1*H*-benzo[*d*]imidazole-2-thiol (**1b**) together with 6-nitro-1*H*-benzo[*d*]imidazole-2-thiol (**1c**) to observe the effect of the electron-donating group and the electron-withdrawing group. The results are presented in Table 3. The methoxy group promoted the reaction to obtain the product with 81% yield (entry 1) while the nitro group greatly weakened the reaction activity as the yield went down to 27% (entry 2). We

Table 2 One-pot procedure for benzo[*d*]imidazo[2,1-*b*]thiazole analogues[a]

Entry	Substrate	Time (h)	Product	Yield[b] (%)
1	 **2a**	6	 **3a**	64
2	 **2b**	5	 **3b**	68
3	 **2c**	6	 **3c**	72
4	 **2d**	3	 **3d**	68
5	 **2e**	4	 **3e**	54
6	 **2f**	5	 **3f**	62
7	 **2g**	5	 **3g**	77
8	 **2h**	6	 **3h**	71
9	 **2i**	5	 **3i**	69
10	 **2j**	3	 **3j**	85
11	 **2k**	5	 **3k**	83
12	 **2l**	12	 **3l**	54
13	 **2m**	10	 **3m**	43
14	 **2n**	9	 **3n**	53

[a] Reaction conditions: 2-mercaptobenzimidazole **1** (1.1 equiv), **2** (1 equiv), Cs_2CO_3 (2.5 equiv), DMSO (5 ml), at 130 °C. [b] Isolated yields.

also explored the reaction with 1-bromo-2-nitrobenzene (entries 3–4). No desired product was detected for substrate **1c**, we could only obtain the initial substituted intermediate and the sequential cyclization step could not take place. 1*H*-imidazole-2-thiol could readily react with 2,3-dichloro-5-(trifluoromethyl) pyridine to generate the expected imidazo[2′,1′ : 2,3]thiazolo[5,4-*b*]pyridine.

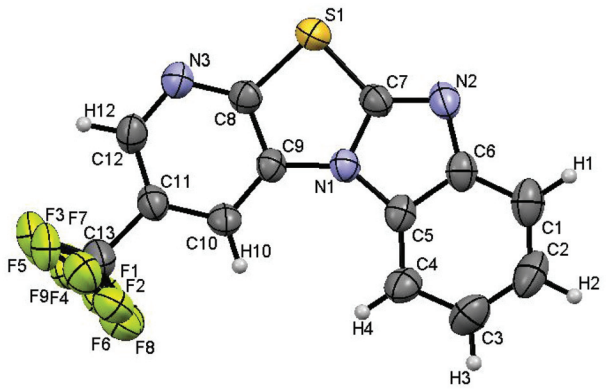


Fig. 2 Single crystal structure of **3a**.†

Conclusion

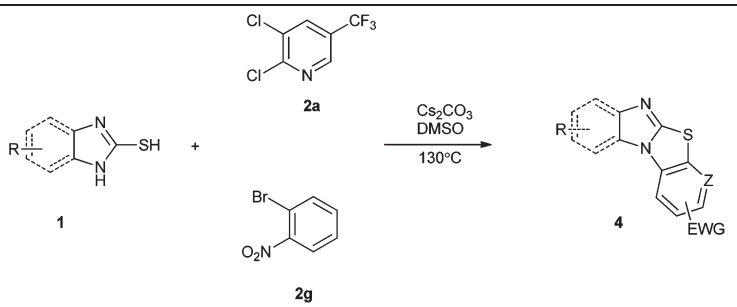
In summary, we developed an economical metal-free procedure to construct benzo[*d*]imidazo[2,1-*b*]thiazole analogues. A series of compounds were synthesized to examine the extension and limitation of the methodology. This approach may have applications in the synthesis of biological and pharmaceutical molecules with benzo[*d*]imidazo[2,1-*b*]thiazole skeletons.

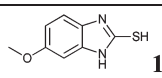
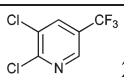
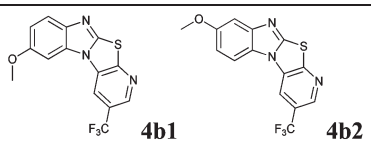
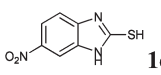
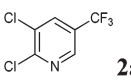
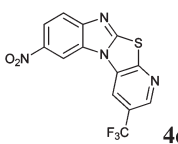
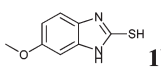
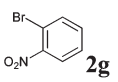
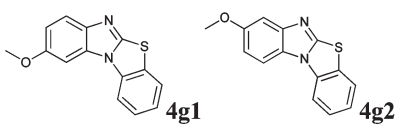
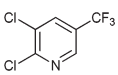
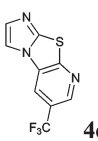
Experimental section

General information

All the reagents were commercially available and were used without further purification. All reactions were monitored by thin-layer chromatography (TLC). ^{1}H NMR spectra were recorded on a Bruker Avance 400 or 300 spectrometer at 400 or

Table 3 Effect of various substituent groups on the methodology[a]



Entry	Substrate **1**	Substrate **2**	Product	Yields[b] (%)
1	 **1b**	 **2a**	 **4b1** **4b2** **6:5**[c]	81
2	 **1c**	 **2a**	 **4c**	27
3	 **1b**	 **2g**	 **4g1** **4g2** **1:1**	79
4	 **1d**	 **2a**	 **4d**	67

[a] Reaction conditions: **1** (1.1 equiv), **2** (1 equiv), Cs_2CO_3 (2.5 equiv), DMSO (5 ml), TLC monitored the reaction to completion, reaction time 4–8 h. [b] Isolated yields. [c] The ratios was obtained using NMR.

300 MHz, using $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal standard. ^{13}C NMR spectra were run *via* the same instrument at 100 or 75 MHz. Melting points were determined on an XD-4 digital micro melting point apparatus. HRMS spectra were determined on a Q-TOF6510 spectrograph (Agilent).

General experimental procedure for 3a

A mixture of **1a** (1.1 mmol), **2a** (1 mmol), Cs_2CO_3 (2.5 mmol) was added to 5 ml DMSO, pre-stirred for several minutes, then the mixture was allowed to heated to 130 °C under the atmosphere of N_2, TLC monitored the end of the reaction. After the mixture was cooled, water was added. The solution was extracted with ethyl acetate (15 × 3). The combined organic phase was dried with $MgSO_4$ and the solvent was removed *in vacuo* to obtain the residue. The residue was purified by column chromatography on silica gel to afford **3a**.

3-(Trifluoromethyl)benzo[4′,5′]imidazo[2′,1′:2,3]thiazolo[5,4-*b*]pyridine (3a). White solid (64%), mp 270–271 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.25 (s, 1H), 7.88–7.94 (m, 2H), 7.44–7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.50 114.62 (d, J = 3.5 Hz) 120.31 121.99 123.15 124.36 124.72 128.57 130.19 141.71 (t, J = 4.3 Hz) 147.24 152.82 156.71. HRMS calcd for ($M + H^+$) 294.0268; found: 294.0292.

Benzo[4′,5′]imidazo[2′,1′:2,3]thiazolo[5,4-*b*]pyridine (3b). Light yellow solid (67%), mp 183–186 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.48 (dd, J = 1.2, 1.5 Hz, 1H), 8.11 (d, J = 8.1 Hz, 1H), 7.85 (dd, J = 1.8 Hz, 1H), 7.36–7.49 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.31 118.22 119.77 121.02 122.50 124.07 128.78 130.23 145.16 146.91 152.53 153.02. HRMS calcd for ($M + H^+$) 226.0394; found: 226.0427.

2-(Trifluoromethyl)benzo[*d*]benzo[4,5]imidazo[2,1-*b*]thiazole (3c). White solid (72%), mp 211–213 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H), δ 7.95–7.99 (m, 1H), 7.58–7.88 (m, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.41–7.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.69 109.07 (q, J = 3.75 Hz) 110.64 119.84 121.09 (q, J = 3.75 Hz) 121.92 122.57 124.17 124.64 125.53 129.57 133.32 148.21 155.18. HRMS calcd for ($M + H^+$) 293.0316; found: 293.0372.

Benzo[*d*]benzo[4,5]imidazo[2,1-*b*]thiazole-2-carbonitrile (3d, 3m). White solid (68%, 43%), mp 274–276 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 1.2 Hz, 1H), 7.94–7.97 (m, 1H), 7.85–7.88 (m, 2H), 7.66 (dd, J = 1.5, 1.2 Hz, 1H), 7.43–7.51 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.78 115.89 118.79 121.71 123.80 124.13 124.46 129.94 133.59 144.16 145.45 147.31 147.82 156.43. HRMS calcd for ($M + H^+$) 250.0394; found: 250.0434.

2-Fluorobenzo[*d*]benzo[4,5]imidazo[2,1-*b*]thiazole (3e). White solid (54%), mp 163–166 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 8.32–8.46 (m, 2H), 8.06–8.14 (m, 1H), 7.76 (dd, J = 2.4, 2.1 Hz, 1H), 7.13–7.52 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 106.54 (d, J = 28.5 Hz) 117.03 (t, J = 16.2 Hz) 123.93 127.15 128.65 (d, J = 2.4 Hz) 131.45 (d, J = 9.7 Hz) 135.08 (d, J = 12 Hz) 152.75 160.90 165.48 167.90. HRMS calcd for ($M + H^+$) 243.0348; found: 243.0375.

Benzo[*d*]benzo[4,5]imidazo[2,1-*b*]thiazole (3f, 3g, 3h). White solid (62%, 77%, 71%), mp 139–141 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.36 Hz, 2H), 7.85 (dd, J = 1.36, 1.28 Hz, 1H), 7.76 (d, J = 8 Hz, 1H), 7.54–7.58 (m, 1H), 7.37–7.46 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.62 112.41 119.45 122.02 123.68 124.35 124.46 126.74 129.05 130.44 133.22 147.94 155.35. HRMS calcd for ($M + H^+$) 225.0442; found: 225.0468.

3-Chlorobenzo[*d*]benzo[4,5]imidazo[2,1-*b*]thiazole (3i). White solid (69%), mp 210–212 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 7.32 Hz, 1H), 7.83 (d, J = 8.56 Hz, 2H), 7.72 (d, J = 1.96 Hz, 1H), 7.51 (dd, J = 2 Hz, 1H), 7.36–7.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.37 112.81 119.68 122.19 123.79 124.07 126.94 129.82 130.25 130.49 131.71 148.08 154.89. HRMS calcd for ($M + H^+$) 259.9989; found: 259.0087.

2-Chlorobenzo[*d*]benzo[4,5]imidazo[2,1-*b*]thiazole (3j). White solid (85%), mp 233–236 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, J = 1.92, 1.32 Hz, 2H), 7.84 (dd, J = 1.32, 1.48 Hz, 1H), δ 7.65 (d, J = 8.52 Hz, 1H), δ 7.37–7.45 (m, 2H), 7.36 (dd, J = 1.92 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.64 112.84 119.63 122.40 124.10 124.65 124.99 127.35 130.21 132.88 133.83 147.89 155.54. HRMS calcd for ($M + H^+$) 259.9989; found: 259.0087.

4-Chlorobenzo[*d*]benzo[4,5]imidazo[2,1-*b*]thiazole (3k). White solid (83%), mp 198–201 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.04 Hz, 1H), 7.84 (t, J = 6.2, 7.64 Hz, 2H), 7.50 (t, J = 8 Hz, 1H) δ 7.34–7.44 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.27 110.51 119.73 122.27 123.90 124.17 127.60 128.92 129.28. 130.36 134.07 148.05 154.63. HRMS calcd for ($M + H^+$) 259.9989; found: 259.0083.

2-Nitrobenzo[*d*]benzo[4,5]imidazo[2,1-*b*]thiazole (3l). Yellow solid (54%), mp 274–277 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.30 (d, J = 8.32 Hz, 1H), 8.05 (d, J = 4.72 Hz, 1H), 7.87–7.92 (m, 2H), 7.50 (d, J = 3.72 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.31 110.82 119.44 120.06 123.15 124.54 124.67 130.32 133.27136.75 146.70 147.91 154.95. HRMS calcd for ($M + H^+$) 270.0293; found: 270.0333.

Benzo[*d*]benzo[4,5]imidazo[2,1-*b*]thiazole-4-carbonitrile (3n). Light yellow solid (53%), mp 232–234 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.05 (d, J = 8 Hz, 1H), 7.34 (dd, J = 1.24 Hz, 1H), 7.82 (m, 2H), 7.39–7.48 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 97.56 114.46 119.10 119.54 122.85 124.28 124.71 128.90 131.21 131.33 132.88 134.91 148.26 154.91. HRMS calcd for ($M + H^+$) 250.0394; found: 250.0433.

7-Methoxy-3-(trifluoromethyl)benzo[4′,5′]imidazo[2′,1′:2,3]thiazolo[5,4-*b*]pyridine (4b1), 8-methoxy-3-(trifluoromethyl)-benzo[4′,5′]imidazo[2′,1′:2,3]thiazolo[5,4-*b*]pyridine (4b2). White solid (81%), mp 225–227 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.14 (d, J = 1.5 Hz), 7.77 (dd, J = 4.2 Hz, 1H), 7.35 (dd, J = 2.4 Hz, 1H), 7.09 (dd, J = 2.4 Hz, 1H), 3.97(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.29 95.09 102.89 110.78 112.56 114.40 (q, J = 3.75 Hz) 120.45 124.57 128.41 130.57 141.66 (t, J = 4.5 Hz) 151.17 156.66 157.82. HRMS calcd for ($M + H^+$) 324.0374; found: 324.0406.

7-Nitro-3-(trifluoromethyl)benzo[4′,5′]imidazo[2′,1′:2,3]thiazolo-[5,4-*b*]pyridine (4c). Yellow solid (27%), mp 241–244 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, J = 0.88 Hz, 1H), 8.75 (d, J = 2.04 Hz, 1H), 8.51 (d, J = 8.84 Hz, 1H), 7.39–7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.78 115.91 118.80 121.73 123.82 124.53 (d, J = 8.4 Hz) 129.94 (d, J = 3.4 Hz) 133.62 144.19 (t, J = 4 Hz) 145.51 147.34 147.86 156.43. HRMS calcd for ($M + H^+$) 339.0119; found: 339.0151.

9-Methoxybenzo[*d*]benzo[4,5]imidazo[2,1-*b*]thiazole (4g1), 8-methoxybenzo[*d*]benzo[4,5]imidazo[2,1-b]thiazole (4g2). White solid (79%), mp 123–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (dd, J = 3.2 Hz, 2H), 8.75 (d, J = 4.8 Hz, 1H), 7.69–7.72 (m, 3H), 7.52 (t, 2H) δ 7.41 (d, J = 2.24 Hz, 1H), 7.31–7.36 (m, 3H), 6.97–7.05 (m, 2H), 3.92 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.13 95.62 102.28 110.77 111.18 111.59 112.14 119.72 124.25 126.58 128.09 133.08 155.74 156.89. HRMS calcd for ($M + H^+$) 255.0547 found: 255.0614.

6-(Trifluoromethyl)imidazo[2′,1′:2,3]thiazolo[5,4-*b*]pyridine (4d). White solid (67%), mp 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.28 (s, 1H), 7.99 (s, 1H), 7.46 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.67 121.40 123.72 125.87 129.89 (q, J = 3.75 Hz) 135.96 143.22 (q, J = 4.5 Hz) 146.32 146.95. HRMS calcd for ($M + H^+$) 244.0112; found: 244.0187.

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