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Solvent-Driven Iodine-mediated Oxidative Strategies for the Synthesis of Bis(imidazo[1,2-*a*]pyridin-3-yl)sulfanes and Disulfanes

S. M. Abdul Shakoor,[a] Devesh S. Agarwal,[a] Sadhika Khullar,[b] Sanjay K. Mandal,[c] and Rajeev Sakhuja*[a]

Abstract: Two efficient, economic, one-pot, iodine-mediated strategies are described to access bis(imidazo[1,2-a]pyridin-3-yl)sulfanes and bis(imidazo[1,2-a]pyridin-3-yl)disulfanes in chloroform and acetic acid respectively, via direct oxidative homocoupling of imidazo-heterocycles using in-expensive sodium sulfide as a sulfur source. These strategies are scalable, and an array of substrates delivered their corresponding stable sulfur bridged imidazo-heterocycles in excellent yields.

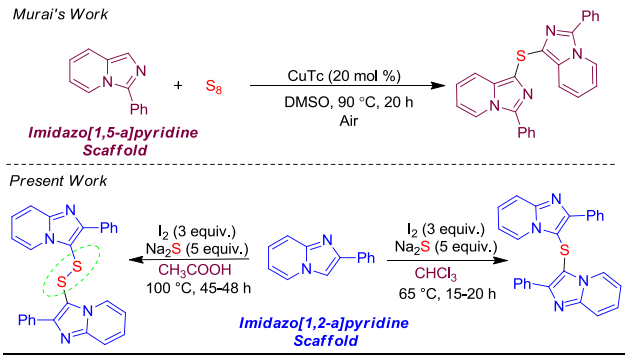
Introduction

Sulfur heterocycles and sulfur-derived functional groups constitute an integral part of numerous natural products and potential pharmaceuticals.[1] Over the years, the accountability of sulfur in about 362 FDA approved drugs has strongly contributed in building up its dominating repute, besides carbon and nitrogen.[2] In particular, sulfide and disulfide linkages are frequently observed in many drugs and bioactive alkaloids such as Discorhabdin B, Butoconazole, Axitinib, Disulfram, Epicorazin B, Emerthallicin E *etc.*[1a,1b,2-3] Disulfide linkages are also responsible for folding and stabilization of tertiary structure of proteins and enzymes.[4] Thus, development of direct synthetic strategies for the construction of C-S-C and C-S-S-C linkages are highly valuable.

With the increasing demand of sustainable chemistry, cross-dehydrogenative coupling strategies leading to the construction of C–C and C–X (X = N, S, O) bonds[5] have streamlined the chemical processes by providing shorter, atom-economical and environmentally benign protocols.[6] The oxidative C−S bond formation is a highly useful, and challenging approach for the construction of sulfur-containing frameworks.[7] A number transition-metal catalyzed[7a,8] and metal-free[9] C–S bond forming strategies have been developed in recent years. Within this realm, molecular iodine has been elegantly employed as an inexpensive and air-insensitive reagent for the oxidative C−S bond formation.[9a,10]

On the other hand, imidazo-heterocycles are well recognized as “privileged scaffolds” due to their eye-catching pharmacological profile.[11] The presence of imidazo[1,2-*a*]pyridine (IP) core in many currently marketed drugs including Alpidem, Olprinone, Minodronic acid, Zolimidine, and optically active GSK812397,[11d, 12] have spurred special interest towards regioselective synthesis of C-3 sulfur decorated imidazo[1,2-*a*]pyridines using disulfides, thiols, sulfenyl chlorides, sulfonyl hydrazines, sodium thiosulfate, sodium sulfonate, DMSO and elemental sulfur as sulfur sources.[13] In 2014, Murai *et al.* demonstrated an interesting protocol for the synthesis of bis imidazo[1,5-*a*]pyridyl sulfides in appreciable yields in presence of CuTC (copper(I) thiophenecarboxylate) using elemental sulfur (Scheme 1).[14a] Very recently, Yasuike *et al.* reported the synthesis of one example of bis[2-(2-iodophenyl)imidazopyridin-3-yl]sulfide in 57% yield under copper-catalyzed conditions using sulfur powder along with the targeted benzothiophene-fused imidazopyridine.[14b] Much prior to these strategies, Glover and coworkers reported the conventional synthesis of bis imidazo[1,5-*a*]pyridyl sulphides & disulphides, and bis imidazo[l,2-*a*]pyridyl disulphides using sulfur dichloride and sulphur monochloride in comparatively lower yields.[14c]

Recently, noticeable efforts have also been made by various research group’s and us towards the synthesis of 3,3'-biimidazo[1,2-*a*]pyridine and methylene linked 3,3'-biimidazo[1,2-*a*]pyridine derivatives.[15] To complement these reports, it became highly desirable to develop environmentally benign protocol for sulfur linked bis-imidazo[1,2-*a*]pyridines as a potential pharmacological lead. Within our continuous program for functionalization of IP,[15f,16] we herein report novel metal-free iodine-mediated strategies for the synthesis of bis(imidazo[1,2-*a*]pyridin-3-yl)sulfanes and disulfanes in different solvent systems, using sodium sulfide as a sulfur source (Scheme 1).



Scheme 1. Previous and the present report on sulfur-bridged dimeric imidazo-heterocycles

Results and Discussion

With an anticipation to synthesize sulfur-bridged dimeric imidazo-heterocycles, and following a trail from our recent report on phenyliodine diacetate (PIDA)-mediated homocoupling of 2-

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arylimidazo[1,2-*a*]pyridines,[15f] we attempted the reaction of 2-phenylimidazo[1,2-*a*]pyridine (**1a**) with 3 equiv. of sodium sulfide (Na_2S) as a model reaction under PIDA-mediated conditions (Table 1, entry 1). Sodium sulfide failed to participate in the reaction, and consequently 3,3'-biimidazo[1,2-*a*]pyridine[15a, 15c-e] was obtained in a variety of solvents under reflux conditions over the targeted 3,3′-bis(imidazo[1,2-*a*]pyridin-3-yl)sulfane (Table 1, entry 1). Moreover, PIDA-mediated reaction of **1a** and Na_2S in dimethyl sulfoxide (DMSO) or *N*,*N*-dimethylacetamide (DMA) failed to yield any product at all (Table 1, entry 2). Interestingly, the desired product bis(imidazo[1,2-*a*]pyridin-3-yl)sulfane (**2a**) was first witnessed and isolated in 18% yield by replacing PIDA with molecular iodine in DCM under ambient conditions (Table 1, entry 3). Interestingly, unexpected formation of bis disulfane **3a** in 10% yield was observed along with **2a** in 48%, when the model reaction was performed using 2 equiv. of iodine in DCM under reflux conditions for 20 h (Table 1, entry 4). The structures of **2a** and **3a** were unambiguously confirmed by ^1H and ^{13}C NMR spectroscopy, HRMS analysis. A further enhancement in the yield of **2a** up to 69% was observed by screening solvents from DCM to DCE, and finally to chloroform under reflux conditions (Table 1, entries 5-6). The reaction was further optimized by varying the number of equivalents of sodium sulfide and iodine. The results indicated that increasing the equivalents of sodium sulfide to five can yield **2a** in 75% yield (Table 1, entry 7). Delightfully, the best result was obtained by using three and five equiv. of molecular iodine and sodium sulfide respectively, yielding 80% of **2a** with trace formation of **3a** (Table 1, entry 8).

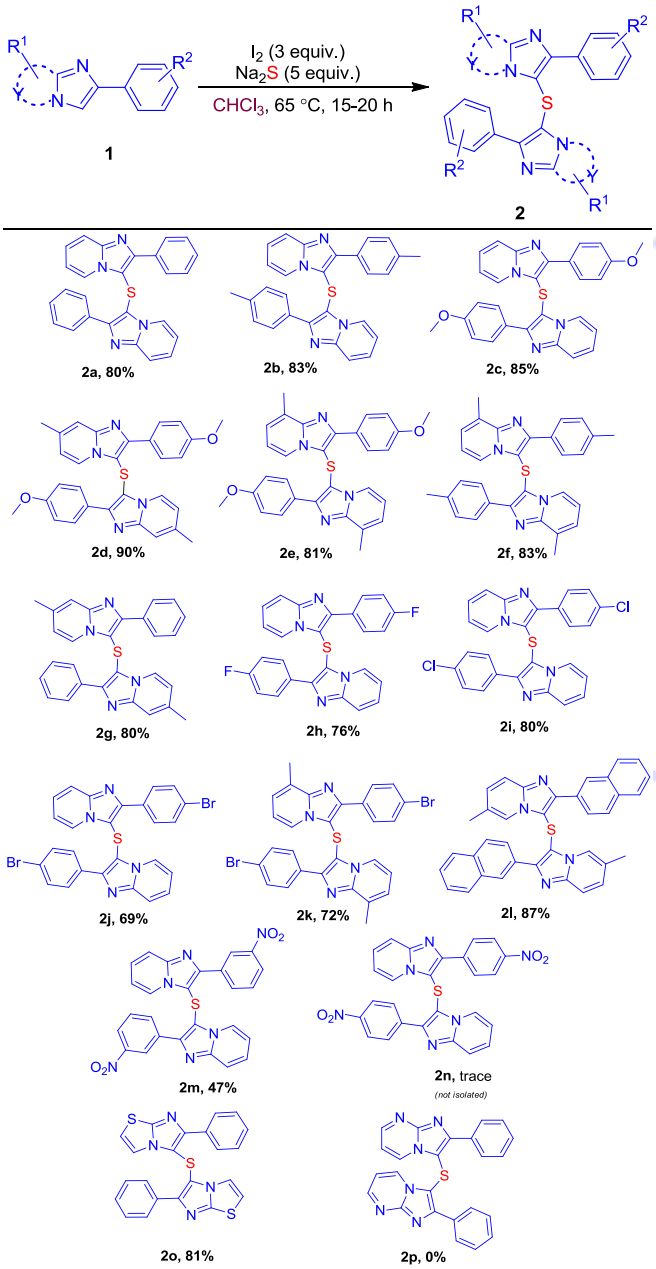
Table 1. Selected Optimization[a] of Reaction Conditions for synthesis of **2a** and **3a**

Entry	Reagent (equiv.)	Sulfur Source (equiv.)	Solvent	Yield[b] (%)	
				2a	**3a**
1[c]	$PhI(OAc)_2$ (2)	Na_2S (3)	DCE/CH_3CN/$CHCl_3$/DCM	-	-
2[d]	$PhI(OAc)_2$ (2)	Na_2S (3)	DMSO/DMA	-	-
3[e]	I_2 (2)	Na_2S (3)	DCM	18	-
4[a]	I_2 (2)	Na_2S (3)	DCM	48	10
5[a]	I_2 (2)	Na_2S (3)	DCE	61	<10
6[a]	I_2 (2)	Na_2S (3)	$CHCl_3$	69	<5
7[a]	I_2 (2)	Na_2S (5)	$CHCl_3$	75	<5
8[a]	**I_2 (3)**	**Na_2S (5)**	**$CHCl_3$**	**80**	**<5**
9[a]	KI (3)	Na_2S (5)	$CHCl_3$	41	<5
10[a]	NH_4I (3)	Na_2S (5)	$CHCl_3$	44	<5
11[a]	I_2 (3)	K_2S (5)	$CHCl_3$	78	<5
12[f]	I_2 (3)	Na_2S (5)	CH_3COOH	<5	47
13[g]	**I_2 (3)**	**Na_2S (5)**	**CH_3COOH**	**<10**	**85**

[a]Reaction conditions: **1a** (0.25 mmol), Reagent (as indicated), Sulfur Source (as indicated), Solvent (5 mL), reflux, 20 h; [b]Isolated yield; [c]T = Boiling point of the solvent for 20 h; [d]T = 110 °C (for 20 h); [e]r.t. for 30 h; [f]T = 100 °C for 20 h; [g]T = 100 °C for 48 h

Subsequently, a number of iodine source replacements such as KI or NH_4I were screened for the reaction, however comparatively lower yields of **2a** were obtained (Table 1, entries 9-10). A marginal decrease in the yield of the **2a** was observed by replacing Na_2S with K_2S (Table 1, entry 11).

With optimized reaction conditions in hand, the practical applicability of the methodology was systematically investigated using various substituted imidazo[1,2-*a*]pyridines bearing electron-donating and electron-withdrawing groups (Scheme 2).



Scheme 2. Substrate scope of substituted 2-arylimidazo-heterocycles towards the synthesis of bis sulfane **2**

2-Arylimidazo[1,2-*a*]pyridine possessing Me and OMe group on the phenyl ring showcased excellent reactivity offering **2b** and **2c** in 83% and 85% yield, respectively. The presence of Me and OMe group on the pyridyl and phenyl rings respectively proved

1d to be the best substrate, producing the corresponding bis sulfane **2d** in 90% yield. Similarly, 2-arylimidazo[1,2-*a*]pyridines bearing Me group on both the pyridyl and phenyl rings yielded their desired bis sulfanes **2f** in 83% yield. Halogen (–F, Cl and Br) substitued 2-phenylimidazo[1,2-*a*]pyridines (**1h-k**) afforded the corresponding products (**2h-k**) in 69-80% isolated yields. The reaction also tolerated bulkier naphthyl group (in place of phenyl) yielding the expected bis sulfane (**2l**) in 87% yield. The *m*-nitro substituted 2-phenylimidazo[1,2-*a*]pyridine (**1m**) showed slight sluggish behavior in reactivity offering **2m** in only 47% yield, whereas *p*-nitro substituted 2-phenylimidazo[1,2-*a*]pyridine (**1n**) showed reluctance in reactivity yielding only trace amount of bis sulfane. This is probably due to the insolubility *p*-NO2-2-phenylimidazo[1,2-*a*]pyridine in chloroform even under reflux conditions. To our delight, the reaction was also successful with 2-phenylimidazo[2,1-*b*]thiazole (**1o**) yielding bis(6-phenylimidazo[2,1-*b*]thiazol-5-yl)sulfane (**2o**) in 81% yield.

Interestingly, during further solvent optimization, 3,3′-bis(imidazo[1,2-*a*]pyridin-3-yl)disulfane (**3a**) was obtained in 47% yield at 100 ^{0}C in acetic acid after 20 h (Table 1, entry 12). Gratifyingly, increasing the reaction time to 48 h in acetic acid at 100 ^{0}C predominantly, yielded **3a** in 85% yield (Table 1, entry 13). Within this realm, the substrate scope of imidazo-heterocycles bearing different electron-donating and electron-withdrawing groups on phenyl and pyridyl rings were examined (Scheme 3). In general, all 2-phenylimidazo[1,2-*a*]pyridine derivatives exhibited admirable reactivity yielding their corresponding disulfanes in excellent yields. Interestingly, the nitro *m*/*p*-substituted 2-phenylimidazo[1,2-*a*]pyridines (**1m-n**) comfortably delivered the desired products (**3m-n**) in 85% and 87% yields, respectively. The methodology was also extended towards the synthesis of 1,2-bis(6-phenylimidazo[2,1-*b*]thiazol-5-yl)disulfane (**3o**) from imidazo[2,1-*b*]thiazole (**1o**) in appreciable yield. Unfortunaltely, 2-phenylimidazo[1,2-*a*]pyrimidine (**1p**) failed to yield either bis sulfane (**2p**) or bis disulfane (**3p**) under optimized conditions. In order to further confirm the proposed structures, as representative examples single crystals of bis sulfane (**2h**) and bis disulfane (**3j** & **3o**) were grown by chloroform for the X-ray diffraction studies.

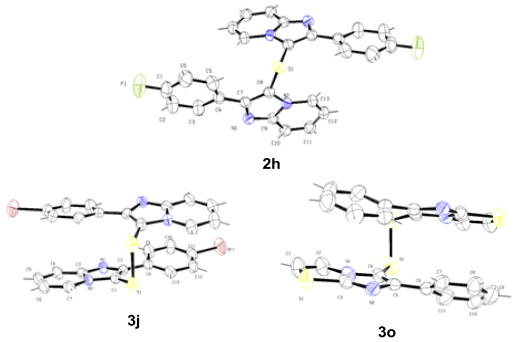
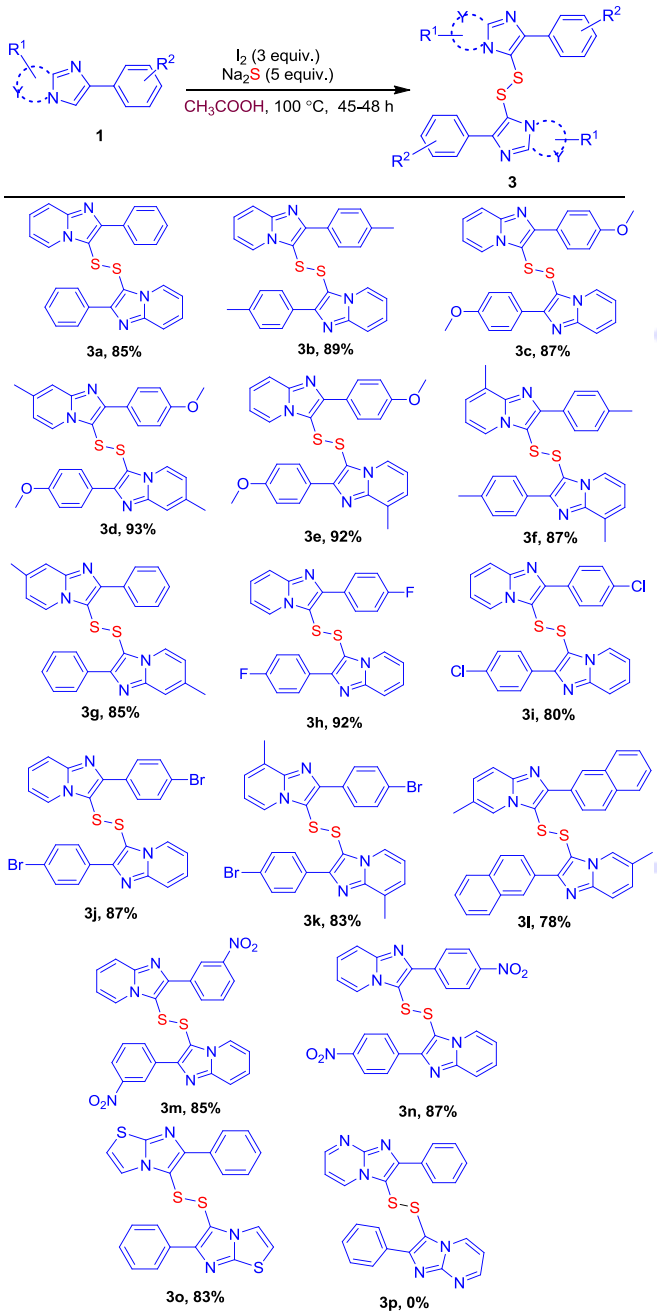


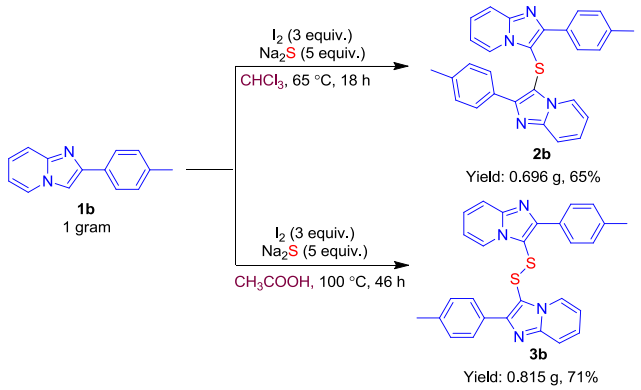
Figure 1. ORTEP diagrams of **2h, 3j, 3o** with 50% thermal probability ellipsoids

Both **2h** & **3j** crystallize in the monoclinic C2/c space group, while **3o** crystallizes in the orthorhombic C2221 space group. ORTEP diagrams of **2h** (CCDC No. 1559710), **3j** (CCDC No. 1559711) and **3o** (CCDC No. 1559712), are shown in Figure 1 (Crystallographic data of **2h**, **3j** and **3o** is provded in SI).



Scheme 3. Substrate scope of 2-phenylimidazo-heterocycles towards the synthesis of bis disulfane **3**

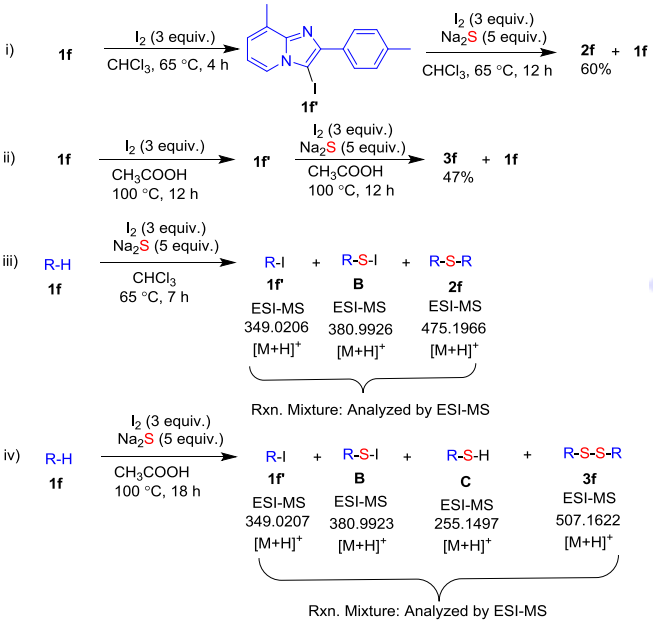
To access the scalability of the developed synthetic strategies, 1 gram scale reactions of 2-(*p*-tolyl)imidazo[1,2-*a*]pyridine (**1b**) with 5 equivalents of sodium sulfide under optimized reaction conditions, yielded bis sulfane (**2b**) and bis disulfane (**3b**) in 65% (0.696 g) and 71% (0.815 g) yields, respectively (Scheme 4).



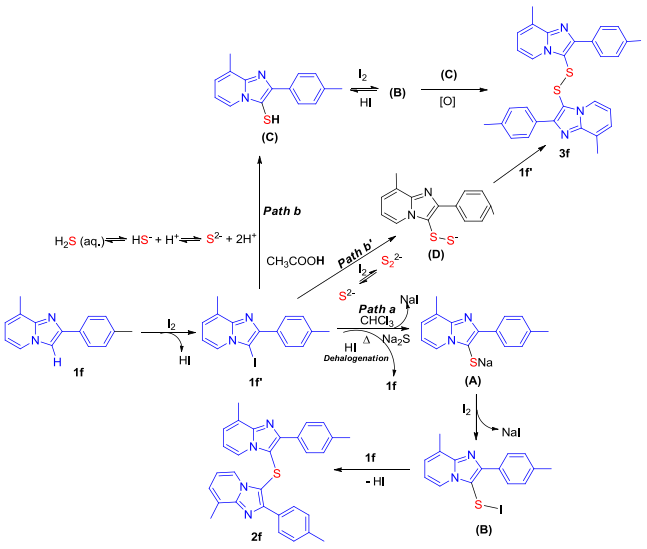
Scheme 4. Gram scale synthesis of bis sulfane (**2b**) & bis disulfane (**3b**)

To probe the reaction mechanism, several preliminary experiments were performed (Scheme 5). 3-iodo-8-methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridine (**1f'**) was observed to be formed (& isolated) in almost quantitative yields (TLC) after refluxing **1f** and I_2 (3 equiv.) in chloroform within 4 h. **1f'** upon further reaction with Na_2S/I_2 in chloroform under reflux conditions resulted in the formation of bis(8-methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)sulfane **2f** in major amounts (Scheme 5i). It is noteworthy to mention that subsequent de-halogenation of **1f'** to **1f** was also observed during the progress of the reaction. Similarly, **1f'** upon reaction with Na_2S/I_2 in acetic acid resulted in the formation of 1,2-bis(8-methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)disulfane **3f** in major amounts, albeit the formation of **1f'** in acetic acid was observed to be a slow process and in lower yield (Scheme 5ii). The mass spectral studies (ESI-MS) of the reaction mixture obtained by reacting **1f** under optimized conditions in chloroform after 7 h affirmed the formation of **1f'**, **B** (R-S-I) and **2f**, thereby suggesting the possible involvement of **B** (R-S- I) intermediate in the reaction pathway (Scheme 5iii). Similarly, the mass spectral studies (ESI-MS) of the reaction mixture obtained by reacting **1f** under optimized conditions in acetic acid after 18 h affirmed the formation of **1f'**, **B, C** and **3f**, thereby suggesting the possible involvement of intermediates **B** (R-S-I) and **C** (R-S-H) in the reaction pathway (Scheme 5iv) (details in supporting information file).

On the basis of our current studies and available literature,[17] a plausible mechanism is proposed (Scheme 6). The initial reaction (in chloroform or acetic acid) is believed to proceed *via* C-3 nucleophilic attack of imidazo[1,2-*a*]pyridine (**1f**) on I_2, forming intermediate **1f'**. In chloroform, the reaction of **1f'** with sulfide ion seems to proceed *via* SNAr mechanism forming intermediate species **A** along with the elimination of NaI. At the same time, the formation of a substantial amount of de-iodinated compound **1f** was also observed (on TLC) during monitoring the progress of the reaction,[18] probably using HI from the reaction mixture. Thereafter, species **A** generates electrophilic species **B** which on further reaction[17a] with **1f** furnishes **2f** (Scheme 6, Path a). On the other hand, due to possible conversion of S^{2-} to either SH^- or H_2S (existing in equilibrium with each other) in acetic acid, the reaction might proceed *via* nucleophilic substitution of I^- in **1f'** by SH^- (or H_2S) to generate thiol intermediate **C** (which is known to exist in equilibrium with **B**).[17b-c] Subsequently, iodine-mediated oxidation[17b,d] of **C** affords **3f** (Scheme 6, Path b). Alternatively, the reaction in acetic acid could also proceed by the nucleophilic attack of *in-situ* generated S_2^{2-} species (by I_2-mediated oxidation of S^{2-}) on **1f'** resulting in **D**, which eventual attacks another **1f'** to yield **3f** (Scheme 6, Path b').



Scheme 5. Preliminary Mechanistic Studies



Scheme 6. Plausible mechanism

Conclusions

In summary, we have successfully described solvent-driven straightforward, direct oxidative strategies for the synthesis of bis(imidazo[1,2-*a*]pyridin-3-yl)sulfanes and bis(imidazo[1,2-*a*]pyridin-3-yl)disulfanes using Na_2S as a sulfur source. This is the first report for the iodine-mediated direct homocoupling of imidazo-heterocycles with sulfur atom(s) linker.

Experimental Section

General

Commercially available reagents were used without purification. Commercially available solvents were dried by standard procedures prior to use. Nuclear magnetic resonance spectra were recorded on 400 MHz spectrometer and chemical shifts are reported in δ units, parts per million (ppm), relative to residual chloroform (7.26 ppm) or DMSO (2.5 ppm) in the deuterated solvent. The following abbreviations were used to describe peak splitting patterns when appropriate: s = singlet, d = doublet, t = triplet, dd = doublet of doublet and m = multiplet. Coupling constants *J* were reported in Hz. The ^{13}C NMR spectra were reported in ppm relative to deuterochloroform (77.0 ppm) or [d_6] DMSO (39.5 ppm). Melting points were determined on a capillary point apparatus equipped with a digital thermometer and are uncorrected. High resolution mass spectra were recorded with a TOF analyzer spectrometer by using electrospray mode.

General procedure for bis sulfane and bis disulfane

A mixture of imidazo-heterocycles (**1a-o**) (0.5 mmol), molecular iodine (1.5 mmol), sodium sulfide (2.5 mmol), in chloroform (10 mL) was refluxed at 65 °C under air atmosphere for 15-20 h. On completion of reaction as indicated by TLC, water was added to the reaction mixture. The organic layer was separated, and washed with a 20% sodium thiosulfate solution (30 mL × 2). The organic layer was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography [SiO_2 (100–200 mesh), hexanes/EtOAc, 8:2 v/v], affording the corresponding bis sulfanes (**2a-o**).

Similarly, a mixture of imidazo-heterocycles (**1a-o**) (0.5 mmol), molecular iodine (1.5 mmol), sodium sulfide (2.5 mmol), in acetic acid (10 mL) was heated at 100 °C under air atmosphere for 45-48 h. On completion of reaction as indicated by TLC, 10% sodium bicarbonate solution (20 mL) was added to the reaction mixture. Thereafter, the reaction mixture was extracted with ethyl acetate (20 mL × 2) and the organic layer was washed with a 20% sodium thiosulfate solution (30 mL × 2). Finally The organic layer was separated, concentrated under reduced pressure and subjected to silica gel column chromatography [SiO_2 (100–200 mesh), hexanes/EtOAc, 3:7 v/v], affording bis sulfanes (**3a-o**).

Bis(2-phenylimidazo[1,2-*a*]pyridin-3-yl)sulfane (2a): White solid; yield: 83 mg (80%); R_f = 0.41 (silica gel, hexanes/EtOAc, 6:4 v/v); mp > 250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.08 (m, 4H), 7.68 – 7.62 (m, 4H), 7.61 – 7.55 (m, 4H), 7.53 (dt, *J* = 9.0, 1.0 Hz, 2H), 7.17 – 7.07 (m, 2H), 6.38 (td, *J* = 6.9, 1.1 Hz, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 146.5, 133.8, 129.6, 128.9, 128.6, 126.4, 125.4, 117.4, 112.6, 107.5, 104.9; HRMS (ESI-TOF) (*m/z*) calculated $C_{26}H_{19}N_4S^+$: 419.1330; found 419.1343 $[M+H]^+$.

Bis(2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)sulfane (2b): White solid; yield: 93 mg (83%); R_f = 0.45 (silica gel, hexanes/EtOAc, 6:4 v/v); mp 244–245 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.1 Hz, 4H), 7.63 – 7.58 (m, 2H), 7.54 – 7.48 (m, 2H), 7.44 (d, *J* = 7.9 Hz, 4H), 7.15 – 7.06 (m, 2H), 6.41 – 6.34 (m, 2H), 2.54 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 146.5, 138.8, 130.9, 129.4, 129.3, 126.2, 125.4, 117.2, 112.5, 106.9, 21.5; HRMS (ESI-TOF) (*m/z*) calculated $C_{28}H_{23}N_4S^+$: 447.1643; found 447.1657 $[M+H]^+$.

Bis(2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)sulfane (2c): White solid; yield: 95 mg (85%); R_f = 0.38 (silica gel, hexanes/EtOAc, 6:4 v/v); mp 220–222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.7 Hz, 4H), 7.64 (d, *J* = 6.9 Hz, 2H), 7.50 (d, *J* = 8.9 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 4H), 7.14 – 7.06 (m, 2H), 6.41 (t, *J* = 6.8 Hz, 2H), 3.97 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 150.6, 146.5, 130.7, 126.3, 126.2, 125.4, 117.2, 114.0, 112.5, 106.5, 55.4; HRMS (ESI-TOF) (*m/z*) calculated $C_{28}H_{23}N_4O_2S^+$: 479.1541; found 479.1538 $[M+H]^+$.

Bis(2-(4-methoxyphenyl)-7-methylimidazo[1,2-*a*]pyridin-3-yl)sulfane (2d): White solid; yield: 117 mg (90%); R_f = 0.35 (silica gel, hexanes/EtOAc, 6:4 v/v); mp 238–239 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.06 (m, 4H), 7.47 (d, *J* = 7.0 Hz, 2H), 7.24 (s, 2H), 7.19 – 7.11 (m, 4H), 6.24 (dd, *J* = 7.0, 1.6 Hz, 2H), 3.97 (s, 6H), 2.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 150.3, 146.8, 137.4, 130.6, 126.46, 124.5, 115.7, 115.0, 113.9, 105.8, 55.4, 21.2; HRMS (ESI-TOF) (*m/z*) calculated $C_{30}H_{27}N_4O_2S^+$: 507.1854; found 507.1873 $[M+H]^+$.

Bis(2-(4-methoxyphenyl)-8-methylimidazo[1,2-*a*]pyridin-3-yl)sulfane (2e): White solid; yield: 121 mg (81%); R_f = 0.36 (silica gel, hexanes/EtOAc, 6:4 v/v); mp 208-209 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.03 (m, 4H), 7.56 – 7.45 (m, 2H), 7.21 – 7.10 (m, 4H), 6.94 – 6.86 (m, 2H), 6.33 (t, *J* = 6.9 Hz, 2H), 3.97 (s, 6H), 2.54 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 150.2, 146.7, 130.9, 127.1, 126.7, 124.9, 123.2, 113.9, 112.3, 107.0, 55.4, 16.7; HRMS (ESI-TOF) (*m/z*) calculated $C_{30}H_{27}N_4O_2S^+$: 507.1854; found 507.1859 $[M+H]^+$.

Bis(8-methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)sulfane (2f): White solid; yield: 98 mg (83%); R_f = 0.44 (silica gel, hexanes/EtOAc, 6:4 v/v); mp 239–240 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.1 Hz, 4H), 7.47 (d, *J* = 6.7 Hz, 2H), 7.42 (d, *J* = 7.9 Hz, 4H), 6.94 – 6.85 (m, 2H), 6.29 (t, *J* = 6.9 Hz, 2H), 2.53 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 146.7, 138.5, 131.2, 129.5, 129.2, 127.2, 124.9 123.3, 112.4, 107.5, 21.5, 16.7; HRMS (ESI-TOF) (*m/z*) calculated $C_{30}H_{27}N_4S^+$: 475.1956; found 475.1977 $[M+H]^+$.

Bis(7-methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)sulfane (2g): White solid; yield: 88 mg (80%); R_f = 0.46 (silica gel, hexanes/EtOAc, 6:4 v/v); mp 203–204 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 – 8.04 (m, 4H), 7.60 – 7.55 (m, 6H), 7.40 (d, *J* = 7.0 Hz, 2H), 7.32 (s, 2H), 6.36 (dd, *J* = 7.0, 1.3 Hz, 2H), 2.21 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.1, 146.5, 138.1, 133.9, 129.3, 129.3, 129.0, 123.9, 116.1, 115.7, 106.4, 20.9; HRMS (ESI-TOF) (*m/z*) calculated $C_{28}H_{23}N_4S^+$: 447.1643; found 447.1640 $[M+H]^+$.

Bis(2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)sulfane (2h): White solid; yield: 86 mg (76%); R_f = 0.52 (silica gel, hexanes/EtOAc, 6:4 v/v); mp >250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 8.6, 5.5 Hz, 4H), 7.60 (d, *J* = 6.9 Hz, 2H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.33 (t, *J* = 8.6 Hz, 4H), 7.16 (dd, *J* = 11.5, 4.3 Hz, 2H), 6.46 (t, *J* = 6.6 Hz, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 162.0, 149.9, 146.5, 131.3, 131.2, 129.9, 126.5, 125.1, 117.5, 115.8, 115.6, 112.7, 106.9; HRMS (ESI-TOF) (*m/z*) calculated $C_{26}H_{17}F_2N_4S^+$: 455.1141; found 455.1165 $[M+H]^+$.

Bis(2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)sulfane (2i): White solid; yield: 97 mg (80%); R_f = 0.58 (silica gel, hexanes/EtOAc, 6:4 v/v); mp >250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.05 (m, 4H), 7.69 – 7.58 (m, 6H), 7.54 (d, *J* = 9.0 Hz, 2H), 7.21 – 7.14 (m, 2H), 6.49 (td, *J* = 6.9, 0.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 146.6, 135.1, 132.2, 130.6, 128.9, 126.7, 125.1, 117.6, 112.9, 107.1; HRMS (ESI-TOF) (*m/z*) calculated $C_{26}H_{17}Cl_2N_4S^+$: 487.0551; found 487.0569 $[M+H]^+$.

Bis(2-(4-bromophenyl)imidazo[1,2-*a*]pyridin-3-yl)sulfane (2j): White solid; yield: 99 mg (69%); R_f = 0.61 (silica gel, hexanes/EtOAc, 6:4 v/v); mp >250°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.4 Hz, 4H), 7.76 (d, *J* = 8.4 Hz, 4H), 7.63 (d, *J* = 6.9 Hz, 2H), 7.54 (d, *J* = 9.0 Hz, 2H), 7.23 – 7.12 (m, 2H), 6.49 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 146.6, 132.7, 131.8, 130.9, 126.7, 125.1, 123.3, 117.6, 113.0, 107.1; HRMS (ESI-TOF) (*m/z*) calculated $C_{26}H_{17}Br_2N_4S^+$: 574.9541; found 574.9552 $[M+H]^+$.

Bis(2-(4-bromophenyl)-8-methylimidazo[1,2-*a*]pyridin-3-yl)sulfane (2k): White solid; yield: 108 mg (72%); R_f = 0.64 (silica gel, hexanes/EtOAc, 6:4 v/v); mp 248-250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.98 (m, 4H), 7.78 – 7.70 (m, 4H), 7.49 (d, *J* = 6.6 Hz, 2H), 6.98 – 6.91 (m, 2H), 6.40 (t, *J* = 6.9 Hz, 2H), 2.54 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 146.8, 133.0, 131.7, 131.1, 127.6, 125.3, 123.1, 122.9, 112.9, 107.5, 16.6; HRMS (ESI-TOF) (*m/z*) calculated $C_{28}H_{21}Br_2N_4S^+$: 602.9854; found 602.9863 $[M+H]^+$.

Bis(6-methyl-2-(naphthalen-2-yl)imidazo[1,2-*a*]pyridin-3-yl)sulfane (2l): White solid; yield: 123 mg (87%); R_f = 0.45 (silica gel, hexanes/EtOAc, 6:4 v/v); mp: >250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 2H), 8.33 (dd, *J* = 8.5, 1.4 Hz, 2H), 8.13 (d, *J* = 8.5 Hz, 2H), 8.70 – 7.97 (m, 4H), 7.61 (dd, *J* = 6.2, 3.2 Hz, 4H), 7.46 – 7.33 (m, 4H), 6.89 (dd, *J* = 9.0, 1.2 Hz, 2H), 1.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 145.6, 133.4, 131.5, 129.5, 128.6, 128.2, 127.8, 127.0, 126.7, 126.5, 123.6, 122.5, 116.5, 107.3, 17.3; HRMS (ESI-TOF) (*m/z*) calculated $C_{36}H_{27}N_4S^+$: 547.1956; found 547.1951 $[M+H]^+$.

Bis(2-(3-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)sulfane (2m): Yellow solid; yield: 59 mg (47%); R_f = 0.60 (silica gel, hexanes/EtOAc, 6:4 v/v); mp: >250°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 2H), 8.47 (d, *J* = 7.6 Hz, 2H), 8.27 (d, *J* = 7.0 Hz, 4H), 7.68 (t, *J* = 8.1 Hz, 4H), 7.42 – 7.30 (m, 2H), 7.02 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 145.4, 135.4, 134.2, 129.4, 126.7, 126.3, 123.2, 122.9, 117.9, 113.8; HRMS (ESI-TOF) (*m/z*) calculated $C_{26}H_{17}N_6O_4S^+$: 509.1032; found 509.1047 $[M+H]^+$.

Bis(6-phenylimidazo[2,1-*b*]thiazol-5-yl)sulfane (2o): White solid; yield: 87 mg (81%); R_f = 0.70 (silica gel, hexanes/EtOAc, 6:4 v/v); mp 230–231 °C; δ 8.09 (dd, *J* = 5.2, 3.3 Hz, 4H), 7.60 – 7.52 (m, 4H), 7.51 – 7.45 (m, 2H), 6.54 (d, *J* = 4.5 Hz, 2H), 6.51 (d, *J* = 4.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 151.2, 133.6, 128.6, 128.5, 118.4, 112.6, 109.4; HRMS (ESI-TOF) (*m/z*) calculated $C_{22}H_{15}N_4S_3^+$: 431.0458; found 431.0475 $[M+H]^+$.

1,2-Bis(2-phenylimidazo[1,2-*a*]pyridin-3-yl)disulfane (3a): Yellow solid; yield: 96 mg (85%); R_f = 0.32 (silica gel, hexanes/EtOAc, 2:8 v/v); mp 242–243 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 6.6 Hz, 2H), 7.78 – 7.50 (m, 4H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.26 – 7.20 (m, 2H), 7.14 (dd, *J* = 12.5, 7.1 Hz, 6H), 6.78 (td, *J* = 6.8, 1.1 Hz, 2H); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 147.3, 131.9, 128.1, 127.9, 127.7, 127.0, 124.4, 117.3, 113.0; HRMS (ESI-TOF) (*m/z*) calculated $C_{26}H_{19}N_4S_2^+$: 451.1051; found 451.1075 $[M+H]^+$. (*Note: In the ^{13}C NMR of most of the bis disulfanes, the numbers of the carbon signals observed are less than the expected number. This is due to the accidental degeneracy of some of the carbons and is been affirmed by ^{1}H-^{13}C correlation spectra of one of the representative compound **3f** (Supporting Information).

1,2-bis(2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)disulfane (3b): White solid; yield: 106 mg (89%); R_f = 0.38 (silica gel, hexanes/EtOAc, 2:8 v/v); mp 203–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 6.5 Hz, 2H), 7.70 – 7.47 (m, 4H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.23 – 7.13 (m, 2H), 6.90 (d, *J* = 6.8 Hz, 4H), 6.77 (td, *J* = 6.8, 0.9 Hz, 2H), 2.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 138.0, 128.4, 127.7, 126.8, 124.4, 117.5, 112.9, 21.3; HRMS (ESI-TOF) (*m/z*) calculated $C_{28}H_{23}N_4S_2^+$: 479.1364; found 479.1387 $[M+H]^+$.

1,2-Bis(2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)disulfane (3c): Yellow solid; yield: 111 mg (87%); R_f = 0.34 (silica gel, hexanes/EtOAc, 2:8 v/v); mp 211–213 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 6.1 Hz, 2H), 7.78 – 7.46 (s, 4H), 7.36 (d, *J* = 7.4 Hz, 2H), 7.25 – 7.18 (m, 2H), 6.79 (t, *J* = 6.7 Hz, 2H), 6.63 (d, *J* = 6.8 Hz, 4H), 3.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 147.3, 129.1, 127.0, 124.5, 117.3, 113.1, 112.9, 55.2; HRMS (ESI-TOF) (*m/z*) calculated $C_{28}H_{23}N_4O_2S_2^+$: 511.1262; found 511.1276 $[M+H]^+$.

1,2-Bis(2-(4-methoxyphenyl)-7-methylimidazo[1,2-*a*]pyridin-3-yl)disulfane (3d): Yellow solid; yield: 125 mg (93%); R_f = 0.30 (silica gel, hexanes/EtOAc, 2:8 v/v); mp 219–220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 6.7 Hz, 2H), 7.78 – 7.39 (m, 4H), 7.17 – 6.92 (m, 2H), 6.75 – 6.45 (m, 6H), 3.81 (s, 6H), 2.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 147.6, 138.4, 129.1, 123.8, 115.9, 115.2, 112.8, 55.0, 21.2; HRMS (ESI-TOF) (*m/z*) calculated $C_{30}H_{27}N_4O_2S_2^+$: 539.1575 ; found 539.1573 $[M+H]^+$.

1,2-Bis(2-(4-methoxyphenyl)-8-methylimidazo[1,2-*a*]pyridin-3-yl)disulfane (3e): Yellow solid; yield: 123 mg (92%); R_f = 0.38 (silica gel, hexanes/EtOAc, 2:8 v/v); mp 221–223 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 3.0 Hz, 2H), 7.75 – 7.70 (m, 4H), 6.97 (d, *J* = 6.8 Hz, 2H), 6.71 (t, *J* = 6.8 Hz, 2H), 6.57 (d, *J* = 5.8 Hz, 4H), 3.78 (s, 6H), 2.48 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 147.5, 128.8, 127.2, 125.7, 124.8, 122.4, 112.6, 112.5, 55.0, 16.7; HRMS (ESI-TOF) (*m/z*) calculated $C_{30}H_{27}N_4O_2S_2^+$: 539.1575; found 539.1572 $[M+H]^+$.

1,2-Bis(8-methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)disulfane (3f): Yellow solid; yield: 110 mg (87%); R_f = 0.51 (silica gel, hexanes/EtOAc, 2:8 v/v); mp 178–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.02 (m, 2H), 7.48 (d, *J* = 7.6 Hz, 4H), 6.99 – 6.92 (m, 2H), 6.84 (d, *J* = 7.7 Hz, 4H), 6.71 (t, *J* = 6.8 Hz, 2H), 2.49 (s, 6H), 2.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 137.2, 129.2, 127.8, 127.5, 127.2, 125.8, 122.4, 112.7, 21.2, 16.7; HRMS (ESI-TOF) (*m/z*) calculated $C_{30}H_{27}N_4S_2^+$: 507.1677; found 507.1683 $[M+H]^+$.

1,2-Bis(7-methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)disulfane (3g): Yellow solid; yield: 102 mg (85%); R_f = 0.46 (silica gel, hexanes/EtOAc, 2:8 v/v); mp 224–225 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 6.9

Hz, 2H), 7.86 – 7.45 (m, 4H), 7.25 – 6.96 (m, 8H), 6.56 (dd, *J* = 6.9, 1.5 Hz, 2H), 2.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 147.6, 138.3, 132.2, 127.9, 127.6, 123.6, 116.2, 115.5, 21.3; HRMS (ESI-TOF) (*m/z*) calculated $C_{28}H_{23}N_4S_2^+$: 479.1364; found 479.1371 $[M+H]^+$.

1,2-Bis(2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)disulfane (3h): White solid; yield: 121 mg (92%); R_f = 0.56 (silica gel, hexanes/EtOAc, 2:8 v/v); mp 227–229 °C; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 8.60 (d, *J* = 6.8 Hz, 2H), 8.31 – 8.23 (m, 4H), 7.54 (d, *J* = 9.0 Hz, 2H), 7.34 – 7.28 (m, 2H), 7.14 – 7.07 (m, 4H), 6.95 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$) *δ* 161.4, 146.4, 130.2, 130.1, 126.9, 125.3, 117.2, 115.4, 115.2, 113.0, 108.5; HRMS (ESI-TOF) (*m/z*) calculated $C_{26}H_{17}F_2N_4S_2^+$: 487.0862; found 487.0880 $[M+H]^+$.

1,2-Bis(2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)disulfane (3i): White solid; yield: 103 mg (80%); R_f = 0.53 (silica gel, hexanes/EtOAc, 2:8 v/v); mp 210–212 °C; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 8.61 (dd, *J* = 6.9, 1.1 Hz, 2H), 8.34 – 8.22 (m, 4H), 7.56 (dd, *J* = 9.0, 1.0 Hz, 2H), 7.45 – 7.37 (m, 4H), 7.34 – 7.26 (m, 2H), 6.99 (td, *J* = 6.8, 1.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$) *δ* 148.1, 146.5, 133.8, 132.6, 129.6, 128.5, 126.9, 125.3, 117.3, 113.1; HRMS (ESI-TOF) (*m/z*) calculated $C_{26}H_{17}Cl_2N_4S_2^+$: 519.0272; found 519.0285 $[M+H]^+$.

1,2-Bis(2-(4-bromophenyl)imidazo[1,2-*a*]pyridin-3-yl)disulfane (3j): Orange solid; yield: 116 mg (87%); R_f = 0.60 (silica gel, hexanes/EtOAc, 2:8 v/v); mp 235–236 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.25 (d, *J* = 6.6 Hz, 2H), 7.49 – 7.29 (m, 8H), 7.10 (d, *J* = 8.1 Hz, 4H), 6.96 – 6.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 147.4, 130.5, 128.9, 127.8, 124.7, 122.5, 117.9, 113.4; HRMS (ESI-TOF) (*m/z*) calculated $C_{26}H_{17}Br_2N_4S_2^+$: 606.9261; found 606.9274 $[M+H]^+$.

1,2-Bis(2-(4-bromophenyl)-8-methylimidazo[1,2-*a*]pyridin-3-yl)disulfane (3k): Yellow solid; yield: 132 mg (83%); R_f = 0.64 (silica gel, hexanes/EtOAc, 2:8 v/v); mp 184–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.18 (d, *J* = 6.2 Hz, 2H), 7.42 (d, *J* = 7.8 Hz, 4H), 7.14 – 7.03 (m, 6H), 6.86 (t, *J* = 6.8 Hz, 2H), 2.51 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 147.5, 130.5, 130.0, 128.7, 127.5, 127.0, 122.5, 121.8, 113.4, 16.7; HRMS (ESI-TOF) (*m/z*) calculated $C_{28}H_{21}Br_2N_4S_2^+$: 634.9574; found 634.9597 $[M+H]^+$.

1,2-Bis(6-methyl-2-(naphthalen-2-yl)imidazo[1,2-*a*]pyridin-3-yl)disulfane (3l): Yellow solid; yield: 113 mg (78%); R_f = 0.47 (silica gel, hexanes/EtOAc, 2:8 v/v); mp 245–247 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.05 (s, 2H), 7.81 (d, *J* = 7.7 Hz, 2H), 7.79 – 7.67 (m, 5H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.56 – 7.36 (m, 5H), 6.74 (d, *J* = 8.4 Hz, 2H), 6.35 (d, *J* = 8.3 Hz, 2H), 2.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 146.2, 133.1, 129.8, 128.6, 127.4, 126.9, 125.9, 125.7, 125.4, 122.8, 122.2, 116.1, 18.2; HRMS (ESI-TOF) (*m/z*) calculated $C_{36}H_{27}N_4S_2^+$: 579.1677; found 579.1673 $[M+H]^+$.

1,2-Bis(2-(3-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)disulfane (3m): Yellow solid; yield: 115 mg (85%); R_f = 0.59 (silica gel, hexanes/EtOAc, 2:8 v/v); mp >250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 9.14 (s, 2H), 8.69 – 8.57 (m, 4H), 8.15 (dd, *J* = 2.3, 1.0 Hz, 2H), 7.63 – 7.57 (m, 4H), 7.35 – 7.28 (m, 2H), 7.00 – 6.92 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$) 148.4, 147.1, 146.7, 135.5, 134.1, 129.4, 127.2, 125.2, 122.9, 122.8, 117.5, 113.4, 109.8; HRMS (ESI-TOF) (*m/z*) calculated $C_{26}H_{17}N_6O_4S_2^+$: 541.0752 ; found 541.0769 $[M+H]^+$.

1,2-Bis(2-(4-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)disulfane (3n): Orange solid; yield: 117 mg (87%); R_f = 0.60 (silica gel, hexanes/EtOAc, 2:8 v/v); mp >250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 8.65 (d, *J* = 6.9 Hz, 2H), 8.59 – 8.53 (m, 4H), 8.28 – 8.22 (m, 4H), 7.61 (d, *J* = 9.0 Hz, 2H), 7.43 – 7.35 (m, 2H), 7.04 (td, *J* = 6.8, 1.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$) *δ* 147.2, 146.8, 140.4, 128.9, 127.5, 125.5, 123.6, 117.6, 113.6, 110.7; HRMS (ESI-TOF) (*m/z*) calculated $C_{26}H_{17}N_6O_4S_2^+$: 541.0752 ; found 541.0778 $[M+H]^+$.

2-Phenyl-3-((6-phenylimidazo[2,1-*b*]thiazol-5-yl)disulfanyl)imidazo[1,2-*b*]isothiazole (3o): Pale yellow solid; yield: 96 mg (83%); R_f = 0.54 (silica gel, hexanes/EtOAc, 2:8 v/v); mp 177–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.80 – 7.77 (m, 4H), 7. 29 – 7.24 (m, 6H), 7.13 (d, *J* = 4.4 Hz, 2H), 6.70 (d, *J* = 4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 154.2, 152.2, 132.4, 128.2, 127.9, 127.3, 117.6, 113.3, 110.1; HRMS (ESI-TOF) (*m/z*) calculated $C_{22}H_{15}N_4S_4^+$: 463.0179; found 463.0164 $[M+H]^+$.

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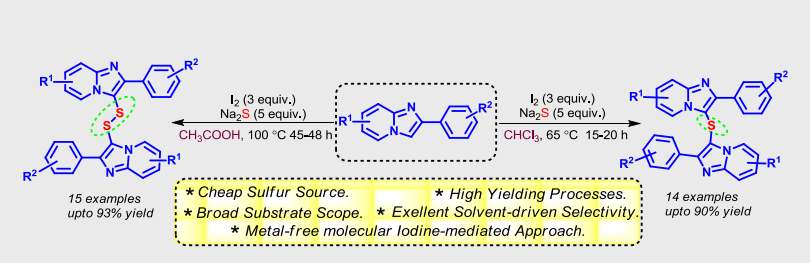

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