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ARTICLE TYPE

Iodine-catalyzed regioselective thiolation of imidazo[1,2-*a*]pyridines using sulfonyl hydrazides as a thiol surrogate

Avik Kumar Bagdi,[a] Shubhanjan Mitra,[a] Monoranjan Ghosh,[a] and Alakananda Hajra*[a]

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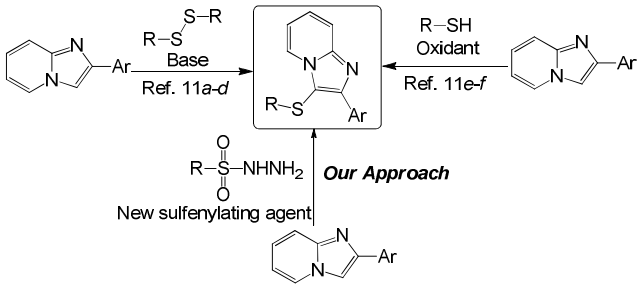
Iodine-catalyzed regioselective sulfenylation of imidazo[1,2-*a*]pyridines *via* C(sp^2)-H bond functionalization has been achieved using sulfonyl hydrazides as a thiol surrogate. A library of 3-sulfanylimidazopyridines with broad functionalities was synthesized under metal and oxidant-free practical reaction conditions. This methodology is also applicable for the regioselective sulfenylation of imidazo[2,1-*b*]thiazole and benzo[*d*]imidazo[2,1-*b*]thiazole.

1. Introduction

Development of new methodologies for the C-S bond formation has gained much attention in organic synthesis due to the occurrences of C-S bond in biologically and pharmaceutically active compounds.[1] The organosulfur compounds are also important for the synthesis of functional materials.[2] Among the organosulfur compounds, aryl and heteroaryl sulfides and their derivatives have wide applications in organic synthesis, pharmaceutical industry as well as in material science.[3] Direct formation of C-S bond *via* C-H functionalization of heterocycles have received considerable attention in recent years, as a potentially more efficient and complementary process to the conventional cross-coupling methodology.[4] Thiols, disulfides, *S*-arylthiophthalimides, sulfonyl chlorides, sodium sulfinates *etc* have been employed as the sulfenylating agents. Very recently, sulfonyl hydrazide has emerged as a new and efficient sulfenylating agent through the cleavage of sulfur-oxygen and sulfur-nitrogen bonds.[5] These are stable solids, odorless, easy to handle and readily accessible compounds. Tian and coworkers first reported the thiolation of indoles employing sulfonyl hydrazides as thiol surrogate.[5a] Subsequently, Singh *et al* also reported the synthesis of vinyl sulfides and diaryl thioethers using sulfonyl hydrazides under microwave irradiation.[5c,d] So far, the employments of sulfonyl hydrazides as sulfenylating agent are limited.

Imidazopyridines are one of the nitrogen containing important fused heterocycles which are found in various marketed drugs and compounds with biological impact.[6] These are also very useful in material science.[7] So, continuous efforts have been paid on the syntheses and functionalizations of the imidazopyridine derivatives.[8] The pharmaceutical property of imidazo[1,2-*a*]pyridine is critically dependent on the nature of the substituents at 3 positions. Incorporation of sulfenyl groups in heterocycle could impart marked biological properties to derivatives like 3-sulfenyl indoles, 3-sulfenyl pyrroles, and 3-sulfenylimidazopyridines which are of considerable therapeutic value against variety of diseases.[9] Imidazo[1,2-*a*]pyridines bearing a thioether side chain at 3 position are highly active against human cytomegalovirus and varicella-zoster virus.[10] However, only few methodologies have been developed for the sulfenylation of imidazo[1,2-*a*]pyridine moieties.[11] Thiols and disulfides have been used as sulphenylating agents in all these cases. The uses of these reagents have some practical limitations such as thiols are foul-smelling, volatile, toxic and disulfides are expensive and moisture sensitive. In addition, these methodologies suffer from some drawbacks like use of transition metal catalyst, stoichiometric amount of oxidants, bases, harsh reaction conditions, and limited applicability. Employment of transition metal catalysts and oxidants generate hazardous wastes which are not desirable from the aspect of green environment. Thus, it would be highly desirable to develop an alternate way for the sulfenylation of imidazo[1,2-*a*]pyridines under transition metal and oxidant-free conditions. In search for an alternate sulfenylating agent with desired synthetic features, we have turned our attention to sulfonyl hydrazides. Ready accessibility and practical usability of sulfonyl hydrazides prompted us to investigate the employment of these reagents as thiol surrogate for the thiolation of imidazopyridines (Scheme 1).



Scheme 1 Thiolation of imidazo[1,2-*a*]pyridines by different sulphenylating reagents

Due to immense importance of imidazopyridines we are also

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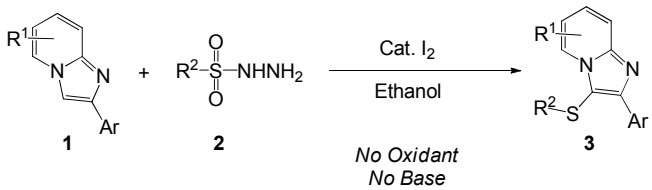
interested about the chemistry of these derivatives. Recently, we have reported various strategies for the synthesis of functionalized imidazopyridine derivatives employing easily accessible chemicals.[12] Based on our experiences on imidazo[1,2-*a*]pyridines and inspired by Tian's pioneering work, we envisaged that imidazo[1,2-*a*]pyiridines could be sulfenylated at 3-position under the practical reaction conditions. Herein, we report a new iodine-catalyzed convenient and regioselective protocol for the sulfenylation of imidazo[1,2-*a*]pyridines employing sulfonyl hydrazides as thiol surrogate in ethanol at 70 ºC (Scheme 2).

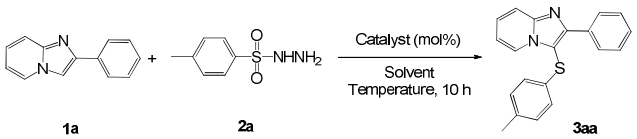


Scheme 2 Regioselective thiolation of imidazo[1,2-*a*]pyridines by sulfonyl hydrazides

2. Results and discussion

The reaction between 2-phenylimidazo[1,2-*a*]pyridine and *p*-toluenesulfonyl hydrazide was taken as the model reaction to optimize the reaction conditions (Table 1). Initially the reaction was carried out using 10 mol% I_2 as catalyst at 60 ºC. Gratifyingly the desired product was obtained with 44% yield after 10 h (Table 1, entry 1). Inspired by this result the reaction temperature was further increased and higher yield was obtained at 70 ºC (Table 1, entries 2-3). After that, catalyst loading was screened to improve the yield. On increasing the catalyst loading to 15, 20, 25 mol%; the desired product obtained with 75, 87, 88% (Table 1, entries 4-6). Thus the catalyst loading was optimized at 20 mol%. Then reaction was performed in different common solvents like MeOH, DMSO, DMF, MeCN *etc* (Table 1, entries 7-15). However no improvement in yields was obtained compared to the EtOH. The reaction proceeded well under solvent-free conditions to afford the product with 68%. For further improvement of the yield, the reaction was carried out using minimum amount of ethanol and in that case the desired product was obtained in 87% yield (Table 1, entry 16). Other iodide sources like TBAI, NIS were not effective like I_2 (Table 1, entries 17-18). Thus the optimized yield (87%) was obtained in presence of 20 mol% I_2 in ethanol (only few drops) at 70 ºC (Table 1, entry 16).

Table 1: Optimization of the reaction conditions[a]



Entry	Catalyst [mol%]	Solvent	Temperature	Yield [%][b]
1	I_2 (10)	Ethanol	60 ºC	44
2	I_2 (10)	Ethanol	70 ºC	64
3	I_2 (10)	Ethanol	reflux[c]	66
4	I_2 (15)	Ethanol	70 ºC	75
5	I_2 (20)	Ethanol	70 ºC	82
6	I_2 (25)	Ethanol	70 ºC	83
7	I_2 (20)	DCE	70 ºC	66
8	I_2 (20)	Toluene	70 ºC	42
9	I_2 (20)	Dioxane	70 ºC	38
10	I_2 (20)	THF	70 ºC	48
11	I_2 (20)	DMSO	70 ºC	47
12	I_2 (20)	DMF	70 ºC	33
13	I_2 (20)	MeCN	70 ºC	36
14	I_2 (20)	EtOAc	70 ºC	24
15	I_2 (20)	-	70 ºC	68
16	I_2 (20)	Ethanol[d]	70 ºC	87
17	TBAI (20)	Ethanol	70 ºC	-
18	NIS (20)	Ethanol	70 ºC	44

[a] Carried out with 0.5 mmol of **1a** and 0.6 mmol of **2a** in the presence of catalyst in solvent (0.5 mL) at 70 ºC for 10 h. [b] Isolated yields. [c] Reaction proceeded under refluxing condition. [d] Only few drops of ethanol (0.1 mL) was used.

With the optimized reaction conditions in hand, substrate scopes of this protocol were investigated and the results are represented in table 2. At first various imidazo[1,2-*a*]pyridines were introduced with *p*-toluenesulfonyl hydrazide under optimized reaction conditions. Imidazo[1,2-*a*]pyridines bearing various substituents like -Me, -Cl at different positions on the pyridine ring efficiently reacted with *p*-toluenesulfonyl hydrazide to afford the desired products with high to excellent yields (**3aa**, **3ba**, **3ca** and **3da**). The imidazo[1,2-*a*]pyridines with electron-donating groups (-Me, -OMe) on the phenyl ring were well tolerated (**3ea** and **3fa**). The imidazo[1,2-*a*]pyridines bearing 2'-hydroxy phenyl substituent produced the desired product with high yields (**3ga**). Halogens (-Cl, -F) containing imidazopyridines afforded the corresponding products with high yields (**3ha** and **3ia**). Strong electron-withdrawing groups like $-NO_2$, $-CF_3$, -CN in the phenyl ring also successfully gave the desired products without any difficulties (**3ja**, **3ka** and **3la**). Imidazo[1,2-*a*]pyridines with heteroaryl substituent also well tolerated under the optimized reaction conditions (**3ma**). Based on the optimization study, the scope of the sulfonyl hydrazides was also studied. The nature of the sulfonyl hydrazides did not have a great effect on the results. When benzenesulfonyl hydrazide was used as reagent, the corresponding product **3bb** was formed in 84% yield. Sulfonyl hydrazides with different substituents (-OMe, -Cl) on the phenyl ring afforded almost comparable yields (**3bc** and **3ad**). It is noteworthy that the aliphatic sulfonyl hydrazides also gave the corresponding products with good yields (**3be**, **3ce** and **3bf**).

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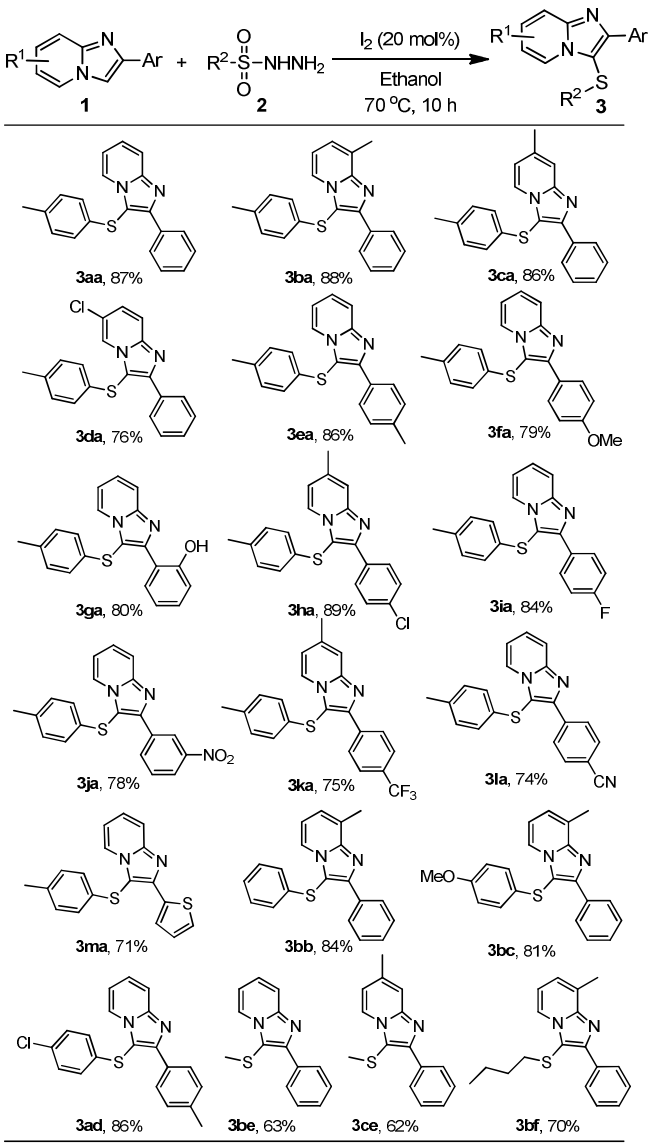
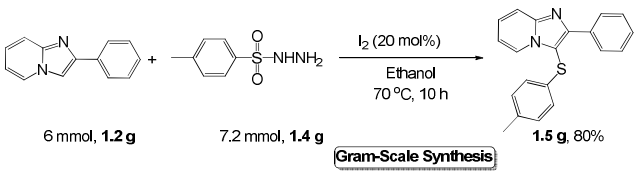
Table 2 Substrates scope for the reaction of imidazopyridines **1** with sulfonyl hydrazides **2**[a]



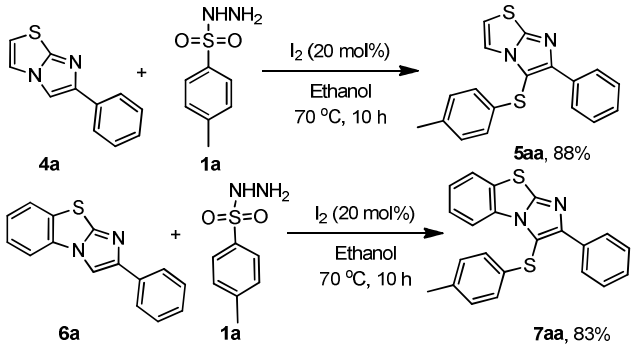
[a] Reaction conditions: 0.5 mmol of **1** and 0.6 mmol of **2** in the presence of I_2 (20 mol%) in EtOH (0.1 mL) at 70 ºC for 10 h, Isolated yields.

The gram-scale reaction was also performed in the usual laboratory setup by taking the reaction of 2-phenylimidazo[1,2-*a*]pyridine with *p*-toluenesulfonyl hydrazide (Scheme 3). This experiment clearly demonstrated the practical applicability of this new protocol for the sulfenylation of imidazopyridines.



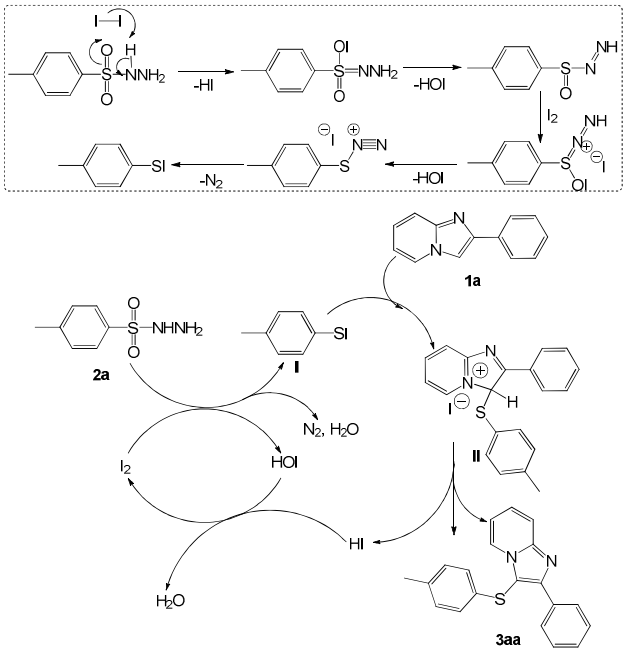
Scheme 3 Synthetic application: Gram-scale reaction

Next we turned our focus to apply this protocol for other imidazoheterocycles. So, imidazo[2,1-*b*]thiazole and benzo[*d*]imidazo[2,1-*b*]thiazole were tested under the optimized reaction conditions. To our delight the corresponding products were obtained with excellent yields (**5aa** and **7aa**) (Scheme 4). It is also notable that only single regioisomer was obtained in case of imidazo[2,1-*b*]thiazole (**4a**) having different nucleophilic sites.



Scheme 4 Regioselective thiolation of imidazoheterocycles

The yield of the reaction (**3aa**, 85%) did not decrease significantly in presence of the radical scavenger TEMPO (3 equiv.) which indicates that the reaction did not take place through a radical pathway. Based on this experiment and the literature reports[5a] a plausible mechanism for the sulfenylation of imidazopyridines has been represented in Scheme 5. Initially, sulfenyl iodide (**I**) is formed by the reaction between sulfonyl hydrazide and I_2 along with the elimination of HOI, H_2O, and N_2. The imidazolenium intermediate **II** is formed by the subsequent electrophilic attack by the sulfur electrophile (**I**) at the 3-position of the imidazopyridine moieties. Finally, the intermediate **II** afforded the desired product by the elimination of HI. This HI reacts with HOI to regenerate the catalyst I_2.



Scheme 5 A plausible reaction mechanism

3. Conclusions

In conclusion, we have developed a new strategy for the regioselective sulfenylation of imidazo[1,2-*a*]pyridines through I_2-catalyzed direct functionalization of sp^2 C-H bond. Use of sulfonyl hydrazides as thiol surrogate has been demonstrated in

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this reaction which occurs through the cleavage of sulfur-nitrogen and sulfur-oxygen bonds. This methodology is applicable to both alkyl and aryl sulfonyl hydrazides, and various imidazopyridines with broad functionalities. Operational simplicity, transition metal and oxidant-free, and environmentally benign reaction conditions, scalable are the attractive features of the present protocol. This methodology is also applicable to imidazo[2,1-*b*]thiazole and benzo[*d*]imidazo[2,1-*b*]thiazole moieties. We believe that our protocol is a versatile and practical alternative to the existing synthetic methodologies for the sulfenylation of imidazoheterocycles.

Experimental

General Methods and Materials

^{1}H NMR spectra were determined on a Bruker 400 (400 MHz) spectrometer as solutions in $CDCl_3$. Chemical shifts are expressed in parts per million (δ) and are referenced to tetramethylsilane (TMS) as internal standard and the signals were reported as s (singlet), d (doublet), t (triplet), m (multiplet) and coupling constants *J* were given in Hz. ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ solution. All reactions were carried out in open air conditions. TLC was done on silica gel coated glass slide (Merck, Silica gel G for TLC). Silica gel (60-120 mesh, SRL, India) was used for column chromatography. Petroleum ether refers to the fraction boiling in the range of 60-80 ^{o}C unless otherwise mentioned. All solvents were dried and distilled before use. Solvents, reagents and chemicals were purchased from Aldrich. All the imidazopyridines were synthesized by following reported methodology.[12*d,f*]

Typical procedure for the synthesis of 2-phenyl-3-*p*-tolylsulfanyl-imidazo[1,2-*a*]pyridine (3aa)[11*d*]:

To a solution of 2-phenyl-imidazo[1,2-*a*]pyridine **1a** (97 mg, 0.5 mmol) in ethanol (0.1 mL), *p*-toluene sulfonylhydrazide **2a** (110 mg, 0.6 mmol) and I_2 (20 mol-%) was added. The mixture was stirred at 70 ^{o}C for 10 h (TLC). After completion, the reaction mixture was cooled to room temperature and ethanol was evaporated. Subsequently, the mixture was extracted with dichloromethane (5 mL) followed by washing with brine (3 mL). The combined organic phases were dried over anhydrous Na_2SO_4. The crude product was concentrated in vacuo and was purified by column chromatography on silica gel using petroleum ether/ethylacetate (15:1 to 10:1) as eluent. Isolated yield: 87%; IR: 3046, 2927, 1638, 1482 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18-8.17 (m, 1H), 8.13-8.11(m, 2H), 7.65-7.62 (m, 1H), 7.36-7.32 (m, 2H), 7.30-7.20 (m, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.83-6.80 (m, 2H), 6.77-6.74 (m, 1H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2, 147.1, 136.1, 133.4, 131.5, 130.3, 128.6, 128.5, 126.7, 125.9, 124.6, 117.7, 113.1, 106.9, 20.9.

8-Methyl-2-phenyl-3-(*p*-tolylthio)*H*-imidazo[1,2-*a*]pyridine (3ba): Isolated yield: 88%; IR: 3042, 2920, 1648, 1479 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 7.6 Hz, 2H), 8.17 (d, *J* = 6.8 Hz, 1H), 7.49-7.46 (m, 2H), 7.42-7.38 (m, 1H), 7.12 (d, *J* = 6.8 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.77 (t, *J* = 6.8 Hz, 1H), 2.75 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8, 147.3, 135.9, 133.7, 131.8, 130.1, 128.5, 128.4, 127.6, 125.8, 125.4, 122.3, 113.0, 107.0, 20.9, 16.8; Anal. Calcd for $C_{21}H_{18}N_2S$: C, 76.33; H, 5.49; N, 8.48%. Found: C, 76.28; H, 5.39; N, 8.39%.

7-Methyl-2-phenyl-3-(*p*-tolylthio)*H*-imidazo[1,2-*a*]pyridine (3ca): Isolated yield: 86%; IR: 3045, 2923, 1645, 1485 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19-8.17 (m, 2H), 8.12 (d, *J* = 6.8 Hz, 1H), 7.48 (s, 1H), 7.44-7.40 (m, 2H), 7.37-7.33 (m, 1H),7.00 (d, *J* = 8.0 Hz, 2H), 6.90-6.88 (m, 2H), 6.68-6.66 (m, 1H), 2.41 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1, 147.5, 137.9, 136.0, 133.6, 131.9, 130.2, 128.5, 128.4, 128.4, 125.8, 123.7, 116.2, 115.7, 106.1, 21.5, 20.9; Anal. Calcd for $C_{21}H_{18}N_2S$: C, 76.33; H, 5.49; N, 8.48%. Found: C, 76.21; H, 5.38; N, 8.34%.

6-Chloro-2-phenyl-3-(*p*-tolylthio)*H*-imidazo[1,2-*a*]pyridine (3da): Isolated yield: 76%; IR: 3045, 2921, 1595, 1488, 1080 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32-8.31 (m, 1H), 8.21-8.18 (m, 2H), 7.66-7.63 (m, 1H), 7.45-7.35 (m, 3H), 7.28-7.25 (m, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.92-6.90 (m, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0, 145.4, 136.5, 133.1, 131.0, 130.4, 128.9, 128.6, 128.4, 128.1, 126.0, 122.6, 121.6, 118.1, 107.9, 21.0; Anal. Calcd for $C_{20}H_{15}ClN_2S$: C, 68.46; H, 4.31; N, 7.98%. Found: C, 68.32; H, 4.20; N, 7.81%.

2-*p*-tolyl-3-(*p*-tolylthio)*H*-imidazo[1,2-*a*]pyridine (3ea): Isolated yield: 86%; IR: 3045, 2920, 1635, 1480 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 6.8 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.29-7.22 (m, 3H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.80 (t, *J* = 6.8 Hz, 1H), 2.36 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2, 147.0, 138.5, 136.0, 131.6, 130.6, 130.2, 129.2, 128.3, 126.5, 125.9, 124.5, 117.5, 112.9, 106.6, 21.4, 20.91; Anal. Calcd for $C_{21}H_{18}N_2S$: C, 76.33; H, 5.49; N, 8.48%. Found: C, 76.30; H, 5.33; N, 8.40%.

2-(4-Methoxyphenyl)-3-(*p*-tolylthio)*H*-imidazo[1,2-*a*]pyridine (3fa): Isolated yield: 79%; IR: 3035, 2929, 2351, 1612, 1477, 1026 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28-8.26 (m, 1H), 8.17-8.15 (m, 2H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.35-7.31 (m, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.92-6.85 (m, 3H), 1H), 3.83 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 150.8, 146.8, 136.2, 131.5, 130.3, 129.8, 126.9, 125.9, 125.7, 124.6, 117.3, 114.0, 113.2, 106.2, 55.4, 21.0; Anal. Calcd for $C_{21}H_{18}N_2OS$: C, 72.80; H, 5.24; N, 8.09%. Found: C, 72.71; H, 5.11; N, 8.01%.

2-(3-(*p*-tolylthio)*H*-imidazo[1,2-*a*]pyridin-2-yl)phenol (3ga): Isolated yield: 80%; IR: 3587, 3024, 2926, 1620, 1485 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.13 (brs, 1H), 8.63 (d, *J* = 8.0 Hz, 1H), 8.33 (d, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 9.2 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.90-6.83 (m, 2H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 149.2, 144.5, 136.4, 130.7, 130.6, 130.3, 127.8, 127.4, 126.2, 124.2, 118.9, 117.7, 116.6, 116.2, 113.7, 106.1, 20.9; Anal. Calcd for $C_{20}H_{16}N_2OS$: C, 72.26; H, 4.85; N, 8.43%. Found: C, 72.11; H, 4.73; N, 8.32%.

2-(4-Chlorophenyl)-7-methyl-3-(*p*-tolylthio)*H*-imidazo[1,2-*a*]pyridine (3ha): Isolated yield: 89%; IR: 3048, 2930, 1598, 1472, 1083 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19-8.16 (m, 2H), 8.12 (d, *J* = 6.8 Hz, 1H), 7.39-7.36 (m, 2H), 7.08 (d, *J* = 6.8 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.74 (t, *J* = 6.8 Hz, 1H), 2.68 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4, 147.3, 136.0, 134.2, 132.2, 131.4, 130.1,

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129.6, 128.5, 127.6, 125.7, 125.4, 122.2, 113.0, 107.2, 20.8, 16.7; Anal. Calcd for $C_{21}H_{17}ClN_2S$: C, 69.12; H, 4.70; N, 7.68%. Found: C, 69.02; H, 4.59; N, 7.52%.

2-(4-Fluorophenyl)-3-(*p*-tolylthio)*H*-imidazo[1,2-*a*]pyridine (3ia): Isolated yield: 84%; IR: 3053, 2920, 2352, 1610, 1479 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.25-8.19 (m, 3H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.32-7.28 (m, 1H), 7.10 (t, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.89-6.81 (m, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1 ($^1J_{C-F}$ = 247 Hz), 150.2, 146.9, 136.2, 131.3, 130.3, 130.2, 129.5, 126.8, 125.8, 124.5, 117.5, 115.4 ($^2J_{C-F}$ = 22 Hz), 113.1, 106.7, 20.9; Anal. Calcd for $C_{20}H_{15}FN_2S$: C, 71.83; H, 4.52; N, 8.38%. Found: C, 71.74; H, 4.43; N, 8.26%.

2-(3-Nitrophenyl)-3-(*p*-tolylthio)*H*-imidazo[1,2-*a*]pyridine (3ja): Isolated yield: 78%; IR: 3083, 2929, 1620, 1519, 1342 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.15-9.14 (m, 1H), 8.59 (d, *J* = 8.0 Hz, 1H), 8.34 (d, *J* = 7.2 Hz, 1H), 8.21-8.18 (m, 1H), 7.74 (d, *J* = 9.2 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.40-7.36 (m, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.94-6.90 (m ,3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 148.2, 147.1, 136.7, 135.3, 134.1, 130.7, 130.4, 129.4, 127.3, 126.3, 124.7, 123.3, 123.1, 117.9, 113.7, 108.6, 21.0; Anal. Calcd for $C_{20}H_{15}N_3O_2S$: C, 66.46; H, 4.18; N, 11.63%. Found: C, 66.31; H, 4.05; N, 11.50%.

3-(*p*-tolylthio)-2-(4-(trifluoromethyl)phenyl)*H*-imidazo[1,2-*a*]pyridine (3ka): Isolated yield: 75%; IR: 3040, 2927, 1588, 1475 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, *J* = 8.0 Hz, 2H), 8.14 (d, *J* = 6.8 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.47 (s, 1H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.69 (d, *J* = 6.4 Hz, 1H), 2.41 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3, 147.5, 138.3, 137.2, 136.3, 131.3, 130.3, 130.1 ($^2J_{C-F}$ = 32 Hz), 128.5, 125.8, 125.3 ($^3J_{C-F}$ = 4Hz), 124.3 ($^1J_{C-F}$ = 271 Hz), 123.8, 116.3, 116.1, 107.2, 21.4, 20.9; Anal. Calcd for $C_{21}H_{15}F_3N_2S$: C, 65.61; H, 3.93; N, 7.29%. Found: C, 65.47; H, 3.84; N, 7.16%.

4-(3-(*p*-tolylthio)*H*-imidazo[1,2-*a*]pyridin-2-yl)benzonitrile (3la): Isolated yield: 74%; IR: 3072, 2925, 2225, 1616, 1483, 1346 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, *J* = 8.4 Hz, 2H), 8.28 (d, *J* = 6.8 Hz, 1H), 7.73-7.67 (m, 3H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.91-6.87 (m, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.5, 147.1, 137.9, 136.5, 132.1, 130.6, 130.4, 128.6, 127.2, 125.9, 124.6, 118.9, 117.8, 113.6, 111.7, 108.5, 20.9; Anal. Calcd for $C_{21}H_{15}N_3S$: C, 73.87; H, 4.43; N, 12.31%. Found: C, 73.79; H, 4.36; N, 12.24%.

7-Methyl-2-(thiophen-2-yl)-3-(*p*-tolylthio)*H*-imidazo[1,2-*a*]pyridine (3ma): Isolated yield: 71%; IR: 3045, 2927, 1641, 1487 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.8 Hz, 1H), 8.00-7.99 (m, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.34-7.32 (m, 1H), 7.27-7.23 (m, 1H), 7.08–7.06 (m, 1H), 6.98–6.92 (m, 4H), 6.80–6.76 (m, 1H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 146.5, 136.3, 136.2, 130.9, 130.1, 127.7, 126.7, 126.5, 126.2, 124.3, 117.3, 113.0, 106.1, 20.9; Anal. Calcd for $C_{19}H_{16}N_2S_2$: C, 67.82; H, 4.79; N, 8.33%. Found: C, 67.71; H, 4.68; N, 8.25%.

8-Methyl-2-phenyl-3-(phenylthio)*H*-imidazo[1,2-*a*]pyridine (3bb)[12f]: Isolated yield: 84%; IR: 3040, 2923, 1643, 1479 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.20–8.18 (m, 2H), 8.07 (d, *J* = 6.8 Hz, 1H), 7.42–7.38 (m, 2H), 7.34–7.30 (m, 1H), 7.16–7.12 (m, 2H), 7.08–7.02 (m, 2H), 6.97–6.94 (m, 2H), 6.68 (t, *J* = 7.2 Hz, 1H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.0, 147.4, 135.5, 133.6, 129.3, 128.5, 128.4, 128.4, 127.6, 125.9, 125.5, 125.4, 122.2, 113.0, 106.4, 16.8.

3-(4-Methoxyphenylthio)-8-methyl-2-phenyl*H*-imidazo[1,2-*a*]pyridine (3bc): Isolated yield: 81%; IR: 3041, 2928, 2343, 1620, 1469, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24–8.22 (m, 2H), 8.11 (d, *J* = 6.8 Hz, 1H), 7.43–7.39 (m, 2H), 7.35–7.33 (m, 1H), 7.01 (d, *J* = 6.8 Hz, 1H), 6.95–6.92 (m, 2H), 6.69–6.65 (m, 3H), 3.61 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 150.2, 146.9, 133.5, 128.5, 128.3, 128.3, 127.8, 127.4, 125.5, 125.4, 122.1, 115.0, 112.9, 108.0, 55.1, 16.7; Anal. Calcd for $C_{21}H_{18}N_2OS$: C, 72.80; H, 5.24; N, 8.09%. Found: C, 72.71; H, 5.13; N, 7.98%.

3-(4-Chlorophenylthio)-2-*p*-tolyl*H*-imidazo[1,2-*a*]pyridine (3ad): Isolated yield: 86%; IR: 3046, 2928, 1580, 1482, 1083 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 6.8 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 9.2 Hz, 1H), 7.35–7.31 (m, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.18–7.14 (m, 2H), 6.92–6.85 (m, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 147.2, 138.8, 133.9, 132.1, 130.2, 129.6, 129.3, 128.3, 126.9, 126.9, 124.3, 117.7, 113.3, 105.5, 21.4; Anal. Calcd for $C_{20}H_{15}ClN_2S$: C, 68.46; H, 4.31; N, 7.98%. Found: C, 68.33; H, 4.22; N, 7.84%.

3-(Methylthio)-2-phenyl*H*-imidazo[1,2-*a*]pyridine (3be): Isolated yield: 63%; IR: 3057, 2918, 1608, 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.41 (d, *J* = 8.8 Hz, 1H), 8.21–8.19 (m, 2H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.43–7.39 (m, 2H), 7.34–7.31 (m, 1H), 7.25–7.21 (m, 1H), 6.89–6.86 (m, 1H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 146.3, 133.7, 128.6, 128.5, 128.4, 128.4, 126.2, 124.4, 117.6, 113.0, 18.3.

7-Methyl-3-(methylthio)-2-phenyl*H*-imidazo[1,2-*a*]pyridine (3ce): Isolated yield: 62%; IR: 3051, 2915, 1612, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 7.2 Hz, 1H), 8.20–8.18 (m, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.34 (s, 1H), 7.31–7.30 (m, 1H), 6.70–6.67 (m, 1H), 2.36 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 146.8, 137.2, 134.0, 128.4, 128.3, 128.2, 123.5, 116.2, 115.4, 21.4, 18.4.

3-(Butylthio)-8-methyl-2-phenyl*H*-imidazo[1,2-*a*]pyridine (3bf): Isolated yield: 70%; IR: 3045, 2912, 1640, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, *J* = 6.8 Hz, 1H), 8.28 (d, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 6.8 Hz, 1H), 6.79 (t, *J* = 6.8 Hz, 1H), 2.66 (s, 3H), 2.60 (t, *J* = 7.2 Hz, 2H), 1.41–1.35 (m, 2H), 1.33–1.24 (m, 2H), 0.73 (t, *J* = 7.2 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0, 146.5, 134.0, 128.5, 128.2, 128.0, 127.4, 124.8, 122.2, 112.7, 110.7, 35.4, 31.4, 21.7, 16.8, 13.5; Anal. Calcd for $C_{18}H_{20}N_2S$: C, 72.93; H, 6.80; N, 9.45%. Found: C, 72.79; H, 6.74; N, 9.34%.

Typical procedure for the synthesis of 6-phenyl-5-(*p*-tolylthio)imidazo[2,1-*b*]thiazole (5aa):

A mixture of 2-phenyl-imidazo[1,2-*a*]thiazole **4a** (100 mg, 0.5 mmol) and *p*-toluene sulfonylhydrazide **2a** (110 mg, 0.6 mmol) was stirred in presence of I_2 (20 mol%) in ethanol (0.1 mL) at 70 ^0C for 10h (TLC). After completion, the reaction mixture was cooled to room temperature and extracted with dichloromethane (5 mL) followed by washing with brine (3 mL) and dried over Na_2SO_4. After evaporation of solvent the crude product was purified by column chromatography on silica gel using petroleum ether/ethylacetate as eluent. Isolated yield: 88%; IR: 3041, 2920, 1620, 1472 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (d , *J* = 7.2 Hz, 2H), 7.40–7.28 (m, 4H), 7.02–6.95 (m, 4H), 6.75 (d , *J* = 4.8

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Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 151.2, 136.2, 133.6, 132.1, 130.2, 128.4, 128.1, 127.5, 126.2, 118.0, 112.9, 108.4, 20.9; Anal. Calcd for $C_{18}H_{14}N_2S_2$: C, 67.05; H, 4.38; N, 8.69%. Found: C, 66.92; H, 4.29; N, 8.57%.

Typical procedure for the synthesis of 2-Phenyl-3-*p*-tolylsulfanyl-benzo[*d*]imidazo[2,1-*b*]thiazole (7aa):

A mixture of 2-phenyl-benzo[*d*]imidazo[2,1-*b*]thiazole **6a** (125 mg, 0.5 mmol) and *p*-toluene sulfonylhydrazide **2a** (110 mg, 0.6 mmol) was stirred in presence of I_2 (20 mol%) in ethanol (0.1 mL) at 70 ^{0}C for 10h (TLC). After completion, the reaction mixture was cooled to room temperature and extracted with dichloromethane (5 mL) followed by washing with brine (3 mL) and dried over Na_2SO_4. After evaporation of solvent the crude product was purified by column chromatography on silica gel using petroleum ether/ethylacetate as eluent. Isolated yield: 83%; IR: 3048, 2926, 1614, 1464 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d , *J* = 8.4 Hz, 1H), 8.11–8.09 (m, 2H), 7.65–7.63 (m, 1H), 7.44–7.37 (m, 2H), 7.34–7.21 (m, 3H), 7.07–7.02 (m, 4H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 150.6, 136.1, 133.5, 133.3, 132.9, 130.4, 130.2, 128.4, 128.3, 127.8, 126.4, 125.8, 124.9, 124.0, 114.5, 110.6, 21.0; Anal. Calcd for $C_{22}H_{16}N_2S_2$: C, 70.93; H, 4.33; N, 7.52%. Found: C, 70.81; H, 4.24; N, 7.43%.

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Notes and references

[a] *Department of Chemistry, Visva-Bharati, Santiniketan-731235, India*
E-mail: alakananda.hajra@visva-bharati.ac.in

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