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Iodine-Mediated Sulfenylation of Imidazo[1,2-*a*]pyridines with Ethyl Arylsulfinates

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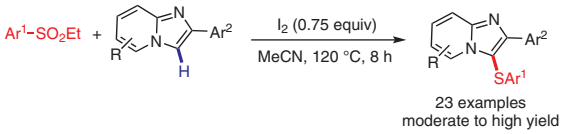

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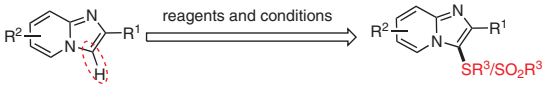
Abstract A simple iodine-mediated approach is reported for the synthesis of sulfenylated imidazo[1,2-*a*]pyridines through the reaction of imidazo[1,2-*a*]pyridines with ethyl arylsulfinates under mild conditions. The reaction scope was investigated, and a plausible mechanism is proposed to elucidate the reaction process and activation mode. The results indicate that ethyl sulfinates are efficient sulfur sources for the construction of C–S bonds.

Key words iodine, ethyl arylsulfinates, sulfenylation, imidazopyridines, arylsulfenylation

Sulfur-containing aromatics and heteroaromatics form a considerable proportion of active compounds among existing natural products; they are also widely used in pharmaceutical formulations and materials science applications,[1] and as precursors of diverse architectures.[2] Generally, the bioactivities and properties of organic molecules depend on the types of substituent groups as well as the core skeleton. The sulfenylation of heteroarenes through substitution reactions is an efficient method for the construction of C–S bonds. Imidazo[1,2-*a*]pyridines are important scaffolds found in natural products[3] and in pharmaceuticals such as zolimidine, alpindem, necopidem, and miroprofen.[4] Consequently, the synthesis of sulfenylated imidazo[1,2-*a*]pyridine molecules has attracted much attention. Over the years, many sulfenylating agents such as sodium sulfinates,[5] sulfonyl hydrazides,[6] sulfenyl chlorides,[7] sulfinic acids,[8] thiols,[9] disulfides,[10] *S*-phenyl sulfonothioates,[11] and sulfur,[12] have been employed for sulfenylation of imidazo[1,2-*a*]pyridines by C–H bond-activation strategies, and these transformations provide efficient synthetic tools for the formation of C-3 substituted imidazo[1,2-*a*]pyridines (Table 1). Alternatively, Guo et al. reported a synthesis of sulfone-substituted imidazo[1,2-*a*]pyridines by treatment with sodium sulfinates[13] and 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct (DAB-

Table 1 Sulfur Sources for Sulfenylation of Imidazo[1,2-*a*]pyridines



Substituents	Reagent	Conditions	[Ref.]
SR^3	R^3SO_2Na	I_2 (1.0 equiv), PPh_3(2 equiv), 80 °C, DMF	4
	$R^3SO_2NHNH_2$	H_2O,140 °C, N_2	5
	R^3SO_2Cl	CuI (10 mol%), PPh_3(3.0 equiv), 130 °C, toluene	6
	R^3SO_2H	eosin B (1 mol%), TBHP (0.8 equiv), 3 W LED, DCE	7
	R^3SH	rose bengal (5 mol%), blue LED, 4Å MS, DMSO	8
		graphene oxide, H_2O, 40 °C	
		NCS (1.5 equiv), CH_2Cl_2	
		5a·TfO (2 mol%), I_2 (4 mol%), MeCN	
	R^3SSR^3	I_2 (5 mol%), DMSO, 90 °C	9
		NBS (2 equiv), –10 °C, DMF	
		NH_4I (10 mol%), AcOH (1 equiv), 110 °C, DMSO–H_2O	
	$R^3S–SO_2R^4$	H_2O, 120 °C	10
	R^3X [X=I, Br, IPh, $I(OAc)_2$]	S_8 (3 equiv), CuI (20 mol%), Na_2CO_3 (4 equiv), 130 °C, DMF	11
SO_2R^3	R^3SO_2Na	I_2 (1.5 equiv), Na_2CO_3 (1.5 equiv), 100 °C, Et_2O	12
	R^3I	DABSO (1.5 equiv), Cu_2O (10 mol%), 130 °C, DMF	13

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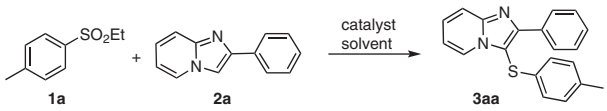
SO) as the sulfur sources.[14] Although these protocols represent considerable advances in the preparation of C3-sulfenylated imidazo[1,2-*a*]pyridines, opportunities remain for the design of methods involving more accessible materials and routines.

Sulfenylation of imidazo[1,2-*a*]pyridines by using the sulfenylating agents discussed above is performed by using a variety of additives, catalysts, and reaction conditions. Despite these significant advances, the development of more useful building blocks in organic transformations to construct C–S bonds is still attractive, and sulfinic esters are also alternative reagents for the introduction of sulfur functional groups in organic synthesis. For instance, a series of sulfonamides[15] and sulfoxides[16] have been prepared by using sulfinic esters; however, alkyl sulfinates have not been explored for the C3-sulfenylation of imidazo[1,2-*a*]pyridines. Here, we report an iodine-mediated selective sulfenylation of imidazo[1,2-*a*]pyridines with ethyl arylsulfinates.

To identify the best reaction conditions, ethyl 4-methylbenzenesulfinate (**1a)** and 2-phenylimidazo[1,2-*a*]pyridine (**2a)** were initially used as the model reactants (Table 2). The reported method for catalyst-free sulfenylation of indoles in ethanol with sulfinic esters[17] was unsuccessful in our case, and the use of hydrazine hydrate[18] as a reducing agent did not improve the situation (Table 2, entries 1 and 2). A further survey of the literature revealed that anhydrides are efficient reagents[19] for the deoxygenation of aryl sulfoxides to the corresponding sulfides. We therefore tested various anhydrides, including trifluoromethanesulfonic anhydride (Tf_2O), polyphosphoric acid (PPA), trifluoroacetic anhydride (TFAA), and acetic anhydride (Ac_2O), in dichloroethane (DCE) at room temperature for eight hours (entries 3–6). Whereas the other anhydrides failed to initiate the reaction, Tf_2O gave the desired product **3aa** in 27% yield. Increasing the temperature to 60 °C (entry 7) reduced the yield to 19%, indicating degradation of reaction components. We therefore discarded the idea of using an anhydride and began to explore other reagents. A combination of iodine and an oxidizing agent has been successfully employed for sulfenylation reactions with sulfinic esters as sulfur sources.[20] When we heated reactants **1a** and **2a** to 120 °C in acetonitrile in the presence of I_2 and di-*tert*-butyl peroxide (DTBP), **3aa** was obtained in 34% yield (entry 8). We later observed that an oxidizing agent is not necessary for this conversion, and a higher yield of 41% was obtained by increasing the molar ratio of I_2 from 10 mol% to 0.5 equivalents (entry 9). With this combination of reaction conditions, we screened various solvents [DMSO, dichloroethane (DCE), 1,4-dioxane, and toluene] and found that that MeCN was the best one (entries 10–13). In an attempt at further improvement, the molar ratio of iodine was increased to 0.75 equivalents, and 51% of the desired product **3a** was isolated (entry 14). Under these reaction conditions [**1a** (1 mmol), **2a** (1 mmol), I_2 (0.75 mmol), MeCN (2 mL), 120 °C], we found that **2a** was not completely consumed, despite prolonging the reaction time to 24 hours. Increasing the amount of **1a** to 2.0 equivalents raised the yield of the desired product **3aa** to 72% (entry 15), with complete consumption of **2a**, as observed by liquid chromatography/mass spectrometry (LC/MS) analysis.

Table 2 Optimization of the Reaction Conditions[a]



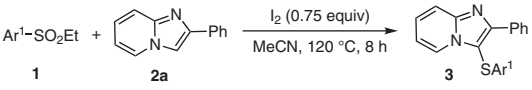
Entry	Catalyst	Solvent	Temp (°C)	Yield[b] (%)
1	–	EtOH	90	0
2	$NH_2NH_2.H_2O$	DMSO	rt	0
3	PPA	DCE	rt	0
4	Ac_2O	DCE	rt	0
5	TFFA	DCE	rt	trace
6	Tf_2O	DCE	rt	27
7	Tf_2O	DCE	60	19
8	I_2 (10 mol%) + DTBP (3 equiv)	MeCN	120	34
9	I_2 (0.5 equiv)	MeCN	120	41
10	I_2 (0.5 equiv)	toluene	120	27
11	I_2 (0.5 equiv)	DCE	120	35
12	I_2 (0.5 equiv)	1,4-dioxane	120	trace
13	I_2 (0.5 equiv)	DMSO	120	trace
14	I_2 (0.75 equiv)	MeCN	120	51
15[c]	I_2 (0.75 equiv)	MeCN	120	72

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), solvent (2 mL), 8 h.
[b] Isolated yield based on **2a**.
[c] **1a** (2 equiv).

With the optimized reaction conditions in hand (Table 2, entry 15), we investigated the substrate scope and limitations of ethyl arylsulfinates for arylsulfenylation of imidazopyridines. As shown in Table 3, a variety of sulfinic esters with various substituents, such as halo, methyl (Me), methoxy (OMe), trifluoromethyl (CF_3), or *tert*-butyl (*t*-Bu) groups were tested and gave the desired products **3ab–am** in yields of 59–88%. Sulfinates with electron-donating groups, such as Me and *t*-Bu, or electron-withdrawing groups, such as CF_3 and Cl, both performed well in this transformation (Table 3, entries 1, 5, 7, and 12). Moreover, sulfinic esters with electron-withdrawing substituents in the *ortho*-position gave better results than those with a similar substituent in the *meta*- or *para*-position (entries 7–9), suggesting the reaction is not affected by steric hindrance. The electronic nature of the aryl group showed an obvious influence on the outcome. As expected, reactants

with bulky groups, such as naphthyl or isobutyl, were well tolerated affording the desired products **3ae** and **3am** in yields of 72 and 59%, respectively (entries 4 and 12).

Table 3 Substrate Scope of Ethyl Sulfones[a]



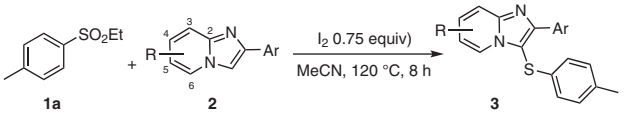
Entry	Ar^1	Product	Yield[b] (%)
1	2-MeC_6H_4	**3ab**	73
2	3-MeC_6H_4	**3ac**	62
3	4-$MeOC_6H_4$	**3ad**	84
4	2-naphthyl	**3ae**	72
5	4-$F_3CC_6H_4$	**3af**	85
6	4-FC_6H_4	**3ag**	70
7	2-ClC_6H_4	**3ah**	88
8	3-ClC_6H_4	**3ai**	73
9	4-ClC_6H_4	**3aj**	65
10	4-BrC_6H_4	**3ak**	60
11	4-IC_6H_4	**3al**	77
12	4-*t*-BuC_6H_4	**3am**	59

[a] Reaction conditions: **1** (2.0 equiv), **2a** (0.2 mmol), I_2 (0.75 equiv), MeCN, 120 °C, 8 h.
[b] Isolated yield based on **2a**.

To further investigate the scope and limitations of this reaction system, a small range of imidazo[1,2-*a*]pyridines were examined under the optimized reaction conditions (Table 4). Generally, substances with substituents such as Me, OMe, CN, F, or Cl gave the corresponding products in moderate to good yields. The electronic nature of substituents on the pyridine ring had no significant effect in the transformation (Table 4, entries 1 and 3). An effect of steric hindrance was obvious in this reaction, and the 4,6-dimethylated reactant gave the corresponding product **3ea** in 49%, probably due to steric hindrance by the group at the C6-position (entries 2 and 4). Imidazo[1,2-*a*]pyridines with substituents such as Me, F, Cl, CN, or OMe on the Ar^2 group reacted smoothly under the optimal reaction conditions, providing the corresponding products in moderate to good yields (entries 6–7 and 9–10), and only the substrate with a cyano group gave **3ia** in a comparatively lower yield (entry 8). Therefore, electronic and steric effects of substituents on the imidazo[1,2-*a*]pyridine are negligible in this protocol.

Next, we performed control experiments to understand the probable reaction mechanism of this sulfenylation reaction (Scheme 2). When ethyl 4-methylbenzenesulfinate (**1a**) reacted with **2a** under the optimized reaction conditions (Scheme 1a), the possible intermediate disulfide **4** was observed by LC/MS. This indicates that the disulfide is a stable key intermediate formed during this process. We

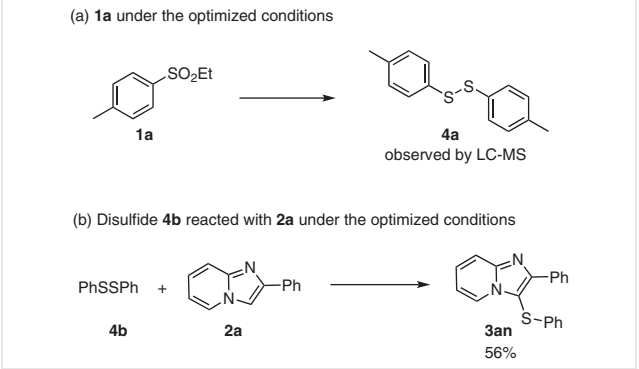
Table 4 Substrate Scope of Imidazo[1,2-*a*]pyridines [a]



Entry	R^1	R^2	Ar	Product	Yield[b] (%)
1	3-Me	H	Ph	**3ba**	71
2	5,6-CH=CH–CH=CH		Ph	**3ca**	57
3	3-Cl	H	Ph	**3da**	64
4	4-Me	6-Me	Ph	**3ea**	49
5	4-Cl	H	Ph	**3fa**	65
6	H	H	4-MeC_6H_4	**3ga**	73
7	H	H	4-FC_6H_4	**3ha**	57
8	H	H	4-NCC_6H_4	**3ia**	49
9	H	H	4-$MeOC_6H_4$	**3ja**	66
10	H	H	4-ClC_6H_4	**3ka**	68

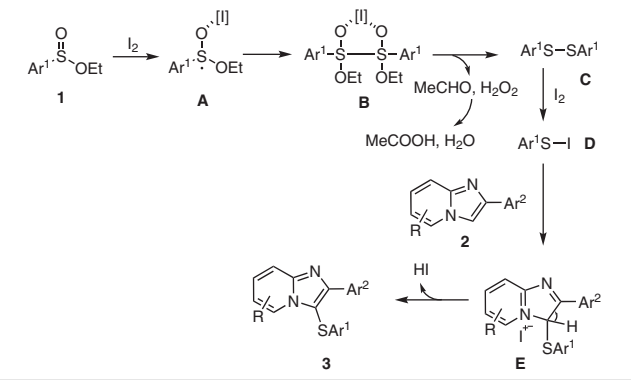
[a] Reaction conditions **1a** (2.0 equiv), **2** (0.2 mmol), I_2 (0.75 equiv), MeCN, 120 °C, 8 h.
[b] Isolated yield based on **2**.

therefore treated commercially available diphenyl disulfide (**4b**) with **2a** under optimized reaction conditions and obtained the corresponding product **3an** in 56% yield (Scheme 1b).



Scheme 1 Primary mechanistic studies

Based on this experimental evidence and previous reports on similar transformations,[16b,19] a plausible mechanism is proposed in Scheme 2. Initially ethyl sulfinate **1** reacts with iodine to generate a radical complex **A**, where iodine might act as a Lewis acid.[16a,20,21] Complex **A** dimerizes to form intermediate **B** through a free-radical reaction, followed by reductive elimination of acetaldehyde and hydrogen peroxide to give disulfide **C**.[18] The byproducts are further transformed into acetic acid and water. Subsequent oxidation of intermediate **C** in the presence of iodine generates intermediate **D**,[13] which is converted into intermediate **E** through regioselective electrophilic attack by



Scheme 2 Proposed mechanism

substrate **2**. The desired product **3** is formed by elimination of HI from intermediate **E**.

In summary, we have developed an efficient iodine-mediated sulfenylation of imidazo[1,2-*a*]pyridines in which an ethyl sulfinate is used as an alternative sulfur source for the construction of a C–S bond.[22] This protocol provides a convenient method for accessing sulfenylated compounds in generally moderate to good yields.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1396-5933.

References and Notes

(1) (a) Zhao, Z.; Pissarnitski, D. A.; Josien, H. B.; Wu, W.-L.; Xu, R.; Li, H.; Clader, J. W.; Burnett, D. A.; Terracina, G.; Hyde, L.; Lee, J.; Song, L.; Zhang, L.; Parker, E. M. *J. Med. Chem.* **2015**, *58*, 8806. (b) Feng, M.; Tang, B.; Liang, S. H.; Jiang, X. *Curr. Top. Med. Chem. (Sharjah, United Arab Emirates)* **2016**, *16*, 1200. (c) Kang, D.; Fang, Z.; Huang, B.; Lu, X.; Zhang, H.; Xu, H.; Huo, Z.; Zhou, Z.; Yu, Z.; Meng, Q.; Wu, G.; Ding, X.; Tian, Y.; Daelemans, D.; De Clercq, E.; Pannecouque, C.; Zhan, P.; Liu, X. *J. Med. Chem.* **2017**, *60*, 4424. (d) Mao, Z.; Yang, Z.; Mu, Y.; Zhang, Y.; Wang, Y.-F.; Chi, Z.; Lo, C.-C.; Liu, S.; Lien, A.; Xu, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 6270. (e) Zhang, C.; Zhu, X. *Acc. Chem. Res.* **2017**, *50*, 1342.

(2) (a) Wang, L.; He, W.; Yu, Z. *Chem. Soc. Rev.* **2013**, *42*, 599. (b) Modha, S. G.; Mehta, V. P.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2013**, *42*, 5042.

(3) (a) DiMauro, E. F.; Kennedy, J. M. *J. Org. Chem.* **2007**, *72*, 1013. (b) Enguehard-Gueiffier, C.; Gueiffier, A. *Mini-Rev. Med. Chem.* **2007**, *7*, 888.

(4) (a) Okubo, T.; Yoshikawa, R.; Chaki, S.; Okuyama, S.; Nakazato, A. *Bioorg. Med. Chem.* **2004**, *12*, 423. (b) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 2832. (c) Ritchie, T. J.; Macdonald, S. J. *J. Med. Chem.* **2014**, *57*, 7206. (d) Kucher, O. V.; Kolodyazhnaya, A. O.; Smolii, O. B.; Nazarenko, N. K.; Kubyshkin, V. P.; Mykhailiuk, K.; Tolmachev, A. A. *Tetrahedron: Asymmetry* **2016**, *27*, 341.

(5) Huang, X.; Wang, S.; Li, B.; Wang, X.; Ge, Z.; Li, R. *RSC Adv.* **2015**, *5*, 22654.

(6) Chowdhury, S. R.; Fadikar, P.; Ul Hoque, I.; Maity, S. *Asian J. Org. Chem.* **2018**, *7*, 332.

(7) Ravi, C.; Mohan, D. C.; Adimurthy, S. *Org. Biomol. Chem.* **2016**, *14*, 2282.

(8) Sun, P.; Yang, D.; Wei, W.; Jiang, M.; Wang, Z.; Zhang, L.; Zhang, H.; Zhang, Z.; Wang, Y.; Wang, H. *Green Chem.* **2017**, *19*, 4785.

(9) (a) Ravi, C.; Chandra Mohan, D.; Adimurthy, S. *Org. Lett.* **2014**, *16*, 2978. (b) Rahaman, R.; Das, S.; Barman, P. *Green Chem.* **2018**, *20*, 141. (c) Iida, H.; Demizu, R.; Ohkado, R. *J. Org. Chem.* **2018**, *83*, 12291.

(10) (a) Ge, W.; Zhu, X.; Wei, Y. *Eur. J. Org. Chem.* **2013**, *2013*, 6015. (b) Rafique, J.; Saba, S.; Rosário, A. R.; Braga, A. L. *Chem. Eur. J.* **2016**, *22*, 11854. (c) Maddi, R. R.; Shirsat, P. K.; Kumar, S.; Meshram, H. M. *ChemistrySelect* **2017**, *2*, 1544. (d) Bettanin, L.; Saba, S.; Doerner, C. V.; Franco, M. S.; Godoi, M.; Rafique, J.; Braga, A. L. *Tetrahedron* **2018**, *74*, 3971.

(11) (a) Ravi, C.; Joshi, A.; Adimurthy, S. *Eur. J. Org. Chem.* **2017**, *2017*, 3646. (b) Reddy, R. J.; Shankar, A.; Kumari, A. H. *Asian J. Org. Chem.* **2019**, *8*, 2269.

(12) (a) Zhu, W.; Ding, Y.; Bian, Z.; Xie, P.; Xu, B.; Tang, Q.; Wu, W.; Zhou, A. *Adv. Synth. Catal.* **2017**, *359*, 2215. (b) Ravi, C.; Reddy, N. N. K.; Pappula, V.; Samanta, S.; Adimurthy, S. *J. Org. Chem.* **2017**, *81*, 9964.

(13) Guo, Y.-J.; Lu, S.; Tian, L.-L.; Huang, E.-L.; Hao, X.-Q.; Zhu, X.; Shao, T.; Song, M.-P. *J. Org. Chem.* **2018**, *83*, 338.

(14) Yang, D.; Sun, P.; Wei, W.; Liu, F.; Zhang, H.; Wang, H. *Chem. Eur. J.* **2018**, *24*, 4423.

(15) (a) Li, G.-J.; Pan, Y.-L.; Liu, Y.-L.; Xu, H.-F.; Chen, J.-Z. *Tetrahedron Lett.* **2019**, *60*, 151260. (b) Ruano, J. L. G.; Parra, A.; Yuste, F.; Mastranzo, V. M. *Synthesis* **2008**, *2008*, 311. (c) Ruano, J. L. G.; Parra, A.; Marzo, L.; Yuste, F.; Mastranzo, V. M. *Tetrahedron* **2011**, *67*, 2905.

(16) (a) Yuste, F.; Hernández Linares, A.; Mastranzo, V. M.; Ortiz, B.; Sánchez-Obregón, R.; Fraile, A.; Garcia Ruano, J. L. *J. Org. Chem.* **2011**, *76*, 4635. (b) Ni, C.; Zhang, L.; Hu, J. *J. Org. Chem.* **2009**, *74*, 3767.

(17) (a) Li, J.; Chen, Y.; Zhong, R.; Zhang, Y.; Yang, J.; Ding, H.; Wang, Z. *Org. Lett.* **2020**, *22*, 1164. (b) Bahrami, K.; Khodaei, M. M.; Karimi, A. *Synthesis* **2008**, *2008*, 2543. (c) Meng, X.; Chen, D.; Cao, X.; Luo, J.; Wang, F.; Huang, S. *Chem. Commun.* **2019**, *55*, 12495.

(18) Yang, X.; Bao, Y.; Dai, Z.; Zhou, Q.; Yang, F. *Green Chem.* **2018**, *20*, 3727.

(19) Zhu, R.-H.; Shi, X.-X. *Synth. Commun.* **2012**, *42*, 1108.

(20) Li, Y.; Zhu, F.; Wang, Z.; Wu, X.-F. *Chem. Asian J.* **2016**, *11*, 3503.

(21) (a) Ji, Y.-Z.; Li, H.-J.; Wang, Y.-R.; Zhang, Z.-Y.; Wu, Y.-C. *Adv. Synth. Catal.* **2020**, *362*, 1039. (b) Nguyen, N.-L. T.; Vo, H.-T.; Duus, F.; Luu, T. X. T. *Molecules* **2017**, *22*, 1458.

(22) **3-(Arylsulfanyl)imidazo[1,2-*a*]pyridines 3aa–am and 3ba–ka; General Procedure**

A sealed tube was charged with the appropriate ethyl arylsulfinate (0.4 mmol), imidazo[1,2-*a*]pyridine (0.2 mmol), I_2 (0.75 equiv), and MeCN (2 mL), and the mixture was stirred at 120 °C for 6 h. When the reaction was complete, the mixture was allowed to cool to r.t. and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 10% EtOAc–PE).

3-[(4-Methylphenyl)sulfanyl]-2-phenylimidazo[1,2-*a*]pyridine (3aa)

Yellow solid; yield: 45 mg (72%); mp 131–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 – 8.14 (m, 3 H), 7.72 (d, *J* = 9.0 Hz, 1 H), 7.49–7.25 (m, 4 H), 7.01 (d, *J* = 8.0 Hz, 2 H), 6.95–6.78 (m, 3 H), 2.24 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.21, 147.04, 136.05, 133.42, 131.51, 130.23, 128.58, 128.43, 128.41, 126.61, 125.84, 124.55, 117.64, 113.04, 106.89, 20.91. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}N_2S$: 317.1107; found: 317.1105.