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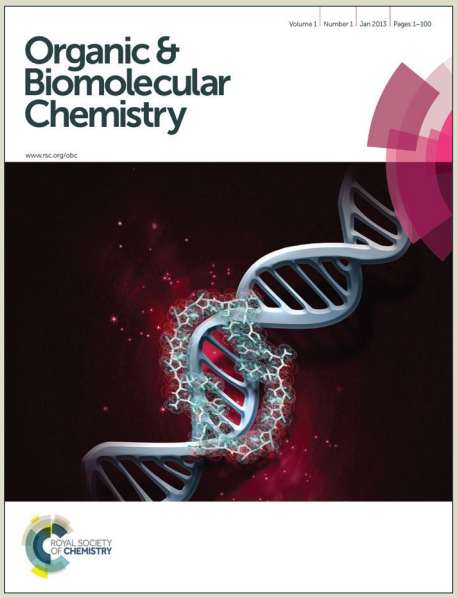

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ARTICLE

Dual Role of *p*–Tosylchloride: Copper–Catalyzed Sulfenylation and Metal free Methylthiolation of Imidazo [1, 2–a] pyridines

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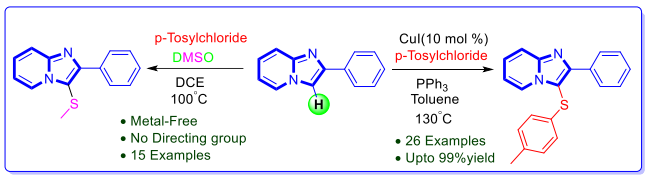
Copper–catalyzed regioselective C–3 sulfernylation of imidazo[1, 2–a]pyridines using *p*-tosylchloride as benign source of sulfernylating agent has been developed. On the other hand, p-tosylchloride mediated thiomethylation of imidazo[1, 2–a]pyridines with dimethylsulfoxide as a source of thiomethylation under metal–free conditions was also described.

Introduction

Selectively substituted imidazo[1,2–a]pyridines represent key structural motifs in medicinal chemistry due to their pharmaceutical activities.[1-6] Particularly C–3 substituted imidazo[1,2–a]pyridine derivatives necopidem, saripidem, and zolpidem are clinically used as neuroactive drugs including other candidates such as alpidem, (as an anxiolytic agent), olprinone (the treatment of acute heart failure), minodronic acid[7] zolimidine (peptic ulcer),[8,9] optically active GSK812397 (HIV infection)[10] (figure S1). Indeed, remarkable progress has been achieved by various groups [11-13] on the synthesis of IP derivatives including our own group.[14-16] Due to the presence of multiple C–H bonds in imidazo[1,2–a]pyridine moiety, it is very challenging for the selective C–3 functionalization. Therefore, there is a continued interest to develop selective C–H (C3) functionalization of these imidazo[1,2–a]pyridine scaffolds.



Scheme 1. Sulfenylation of Imidazo [1, 2–a] pyridines

In particularly the insertion of sulfenyl groups on the aza-aromatic rings can impart marked biological activities.[17,18] Compared to C-3 arylation/alkylation of imidazo[1,2–a]pyridines,[19] the corresponding sulfenylation is rarely reported.[20,21] However, the reported synthetic approaches have some drawbacks such as use of thiols as sulfenyl agent is hazardous (possess unpleasant odors) very difficult to handle, also unstable to air and moisture.[22] Some of the sulfenylating reagents such as sulfenylhydrazides are not commercially available and also expensive.[23] Our intention was to develop a method for the selective C–3 sulfenylation of imidazo[1,2-a]pyridines using cheap and easily available starting materials and reagents and can be performed under mild reaction conditions. Here, we disclose copper-catalysed selective sulfenylation of imidazo[1,2–a]pyridines with tosyl chlorides as benign source of sulfenylating agent and we also demonstrated that transition metal-free methylthiolation of imidazo[1,2–a]pyridines using dimethyl sulfoxide as a source of thiomethylating agent under mild reaction conditions.

Results and discussion

We initially started our investigation by employing commercially available of 2-phenylimidazo[1,2–a]pyridine **1a** with 4-methylbenzene-1-sulfonyl chloride (*p*-TsCl) **2a** as the model substrates (Table 1). The reaction of **1a** with **2a** in NMP as a solvent at 65°C using CuI as a catalyst in a closed tube, traces of desired product 2-phenyl-3-(p-tolylthio)imidazo[1,2–a]pyridine **3a** was observed (Table 1, entry 1). Increase of the reaction temperature to 100 °C, the yield of **3a** was increased to 35% (Table 1, entry 2). Under these conditions, CuI replaced by CuBr, no product was observed (Table 1, entry 3). With t-BuOK (20 mol %) and 1, 10-phenanthroline were employed as an additive and ligand, no product formation and 30% of **3a** was observed respectively (Table 1, entries 4 and 5). Conducting the reaction under oxygen atmosphere (balloon), and in open air trace amount of product formation was observed (Table 1, entries 6 and 7). Increasing the temperature (120 °C) and catalyst loading (20 mol%) the yield of **3a** was increased to 62% (Table 1, entries 8–10). Further increase of temperature (140 °C) no improvement in yield was observed (Table 1, entry 11).[24] Also checked with CuCl, CuBr and without Catalyst but no product formation was observed(Table 1, entries 12–14). Then we screened different catalysts such as I_2, NCS, NBS, NIS, Cu(0), $Cu(OAc)_2$ iron salts like $FeCl_2$, $FeCl_3$, $Fe(OTf)_2$ and $Pd(OAc)_2$ in

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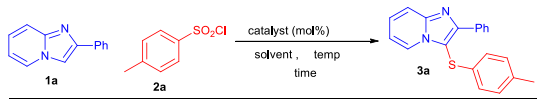
these cases either no reaction of low yields were observed (Table 1, entries 15–24). When PPh_3 was used as reducing agent[25] as well as a ligand at 130°C, 65% yield of **3a** was observed (Table 1, entry 25). Using 3 equivalent of **2a** (w.r.t. **1a**), surprisingly an excellent yield of **3a** was 95% obtained (Table 1, entry 26). To check the efficiency of the reaction under these conditions, but without catalyst (CuI) no reaction was observed (Table 1, entry 27).

Under these optimized conditions (Table 1, entry 26), the reaction of unsubstituted imidazo[1, 2–a]pyridine **5** was subjected with standard conditions (entry 26), the selective C-3 sulfenylated product **5a** was isolated in 24% yield (Scheme 2, eq. 1). When C-3 substituted substrate 3-methylimidazo[1,2-a]pyridine **8** was subjected to the same reaction conditions, the formation desired product **8a** was not observed (Scheme 2, eq. 2).

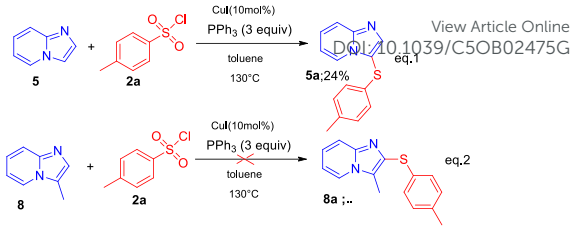
Table 1. Optimization of Reaction Conditions for **3a**[a]



Entry	p-Tosyl chloride(eq)	Catalyst (mol%)	Solvent (mL)	Temp (°C)	Yield(%)
1	1.5	CuI (5)	NMP	65	trace
2	1.5	CuI (5)	NMP	100	35
3	1.5	CuBr (5)	NMP	100	nr
4[b]	1.5	CuI (5)	NMP	100	nr
5[c]	1.5	CuI (5)	NMP	100	30
6[d]	1.5	CuI (5)	NMP	100	trace
7[e]	1.5	CuI (5)	NMP	100	trace
8	2	CuI (5)	NMP	120	54
9	2	CuI (10)	NMP	120	62
10	2	CuI (20)	NMP	120	62
11	2	CuI (10)	NMP	140	53
12	2	CuCl (10)	NMP	120	nr
13	2	CuBr (10)	NMP	120	nr
14	2	–	NMP	120	nr
15	2	I_2 (10)	NMP	120	nr
16	2	NCS (10)	NMP	120	nr
17	2	NBS (20)	NMP	120	nr
18	2	NIS (10)	NMP	120	nr
19	2	Cu(0) (10)	NMP	120	40
20	2	$Cu(OAc)_2$ (10)	NMP	120	45
21	2	$FeCl_2$ (10)	NMP	120	30
22	2	$FeCl_3$ (10)	NMP	120	34
23	2	Fe(OTf) (10)	NMP	120	42
24	2	$Pd(OAc)_2$ (10)	NMP	120	nr
25[f]	2	CuI (10)	Toluene	130	65
26[f]	**3**	**CuI (10)**	**Toluene**	**130**	**95**
27[f]	3	–	Toluene	130	nr

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.75 mmol),CuI(10mol%), PPh_3(0.75mmol), toluene (2mL), 130°C, Closed tube, 24 h, isolated yields. [b] t-BuOK(20 mol%), [c] 1,10-phenanthroline (20 mol%), [d]O_2-balloon, [e] open air. [f] PPh_3(3eq), nr: No reaction.

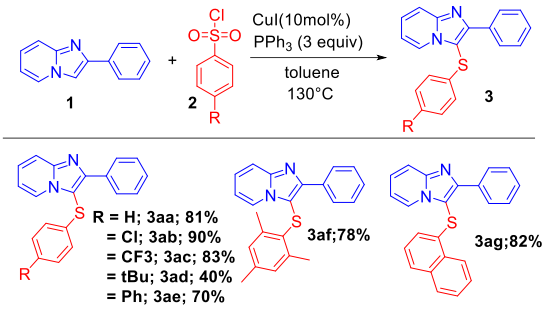
With an optimized catalytic system in hand (Table 1, entry 26), next we investigated the influence of different sulfonyl chlorides 2 on the sulfenylation of imidazo[1,2–a]pyridine 1 (Table 2). The benzenesulfonyl chlorides having different substituent groups at para positions of arene ring including



Scheme 2. Selectivity experiments

2,4,6-trimethylbenzenesulfonyl chloride and naphthalene-1-sulfonyl chloride react smoothly and afford the corresponding sulfenylated imidazo[1,2–a]pyridines **3aa–3ag** with yields ranging from 40% to 90%. Under the optimized conditions, the scope for sulfenylation of substituted imidazo[1,2–a]pyridines and related substrates with 4-methylbenzenesulfonyl chloride was examined (Table 3). The reaction of 4-methylbenzene-1-sulfonyl chloride **2a** with methyl and halogen (Br and Cl)

Table 2. Scope of different sulfonyl chlorides on sulfenylation of **1a**



[a]Reaction conditions: **1** (0.25 mmol), **2** (0.75 mmol), CuI(10mol%), PPh_3(0.75 mmol), toluene (2 mL), 130°C, closed tube, isolated yields.

substituted phenylimidazo[1, 2–a]pyridines under the optimized conditions gave selectively C-3 sulfenylated products **3b-3e** in excellent yields (81-98%). Bromo and methyl disubstituted phenylimidazo[1, 2–a]pyridine also afford the corresponding C–3 sulfenylated product **3f** in good yield. Then we focused on sulfenylation of phenyl ring substituted imidazo[1, 2–a]pyridines.

The presence of electron-donating groups (Me, Et, OMe and SMe) at *para* and *ortho* position of phenyl ring could react smoothly with **2a** and afford the selective C–3 sulfenylated products **3g–3k** up to 92% yields. Surprisingly, ortho-dimethoxyphenyl derivative gave quantitative yield of desired sulfenylated product **3l** despite its steric hindrance. Further, the presence of electron withdrawing groups (such as CN) at either *ortho*/*para*-position of the phenyl ring 2-phenylimidazo[1,2–a]pyridines provided desired products **3m–3p** in good to excellent yields (60-92%).

The present system is also applicable to heterocyclic and alkenyl substituted derivatives 2-(thiophen-2-yl)imidazo[1,2– a]pyridine 3q and (E)-2-styrylimidazo[1,2–a]pyridine 3r, and obtained in 65% and 85% yields respectively. Interestingly, other heterocyclic compounds like 2-phenylbenzo[d]imidazo[2,1–b]thiazole also reactive with 2a under the present conditions and yield the desired product 3s in 52% yield.

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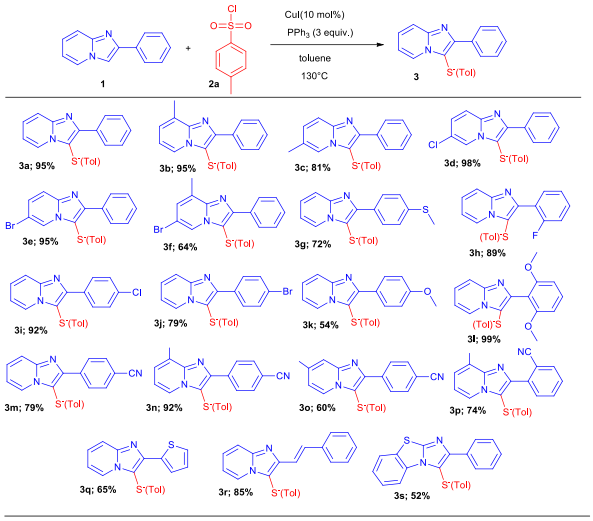
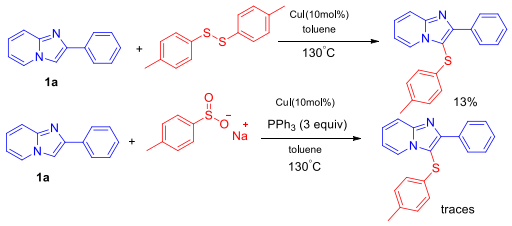
Table 3. Scope for sulfenylation of imidazo[1,2–a]pyridines with **2a**

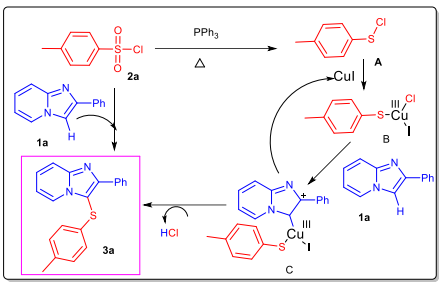


[a]Reaction conditions: **1** (0.25 mmol), **2a** (0.75 mmol), CuI(10 mol%), PPh_3(0.75 mmol), toluene (2.0 mL), 130°C, Closed tube, isolated yields.

The present method not only demonstrates the high degree of functional group tolerance with broad substrate scope, but also overcomes the electronic and steric factors associated with substituent groups.



Scheme 3. Control experiments

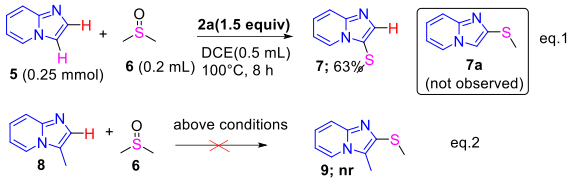


Scheme 4. Plausible mechanism

To ascertain the reaction mechanism, some control experiments were performed (Scheme 3). Reactions with diphenyl disulfide and sodiumsulfinate as sulfenylating agents in place of **2a** under the optimised conditions, only 13% and traces amount of desired product **3a** was isolated respectively (Scheme 3). These reactions suggest that, **2a** is a better sulfenylating agent for the present transformation.

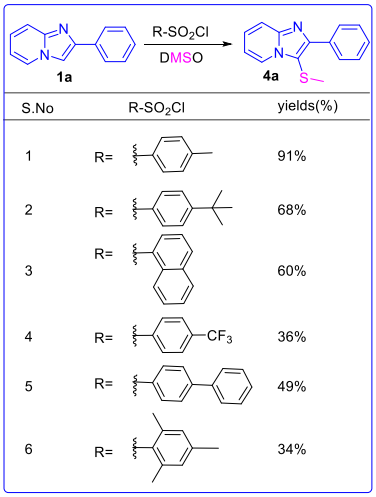
Based on the literature reports[18] and our observations, a probable reaction mechanism has been proposed (Scheme 4).[26-28] Initially, when 4-methylbenzene-1-sulfonyl chloride was heated in presence of PPh_3 at the high temperature it generates p-tolylhypochlorothioite intermediate **A**.[18] Intermediate **A** in presence of CuI undergo oxidative addition to form the highly electrophilic Cu(III) complex **B**. Nucleophilic addition of **1a** to the complex **B** generates carbocation intermediate **C.** Subsequent oxidation of **C** yield the desired product sulfenylimidazo[1,2–a]pyridine **3a**.

During the course of solvent optimization studies for sulfenylation of imidazopyridines (Table S1, entries 11 and 12), the formation of methylthiolated imidazo[1,2–a]pyridine **4a** was isolated in 30 and 39% yields respectively when DMSO was used as solvent under the conditions studied. In these studies, DMSO was act as thiomethanol source. When we checked the literature reports for methylthiolation of heterocyclic compounds, very few reports existed with transition metal catalysts[29-30] and in presence of strong acidic conditions.[31]



Scheme 5. Selectivity experiments

Table 4. Screening of different sulfonylchlorides[a]



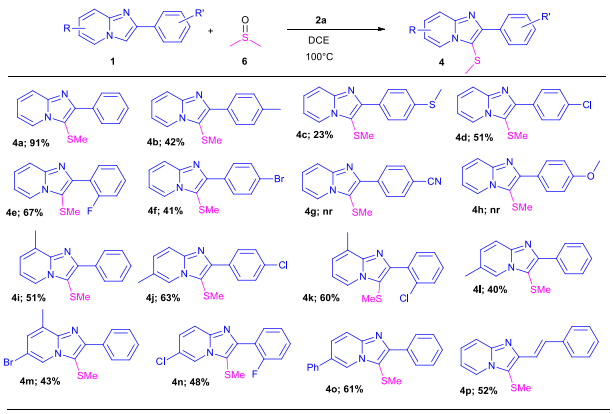
[a]Reaction conditions: 2-phenylimidazo[1,2-a]pyridine (0.25 mmol), tosylchloride (0.375 mmol),DMSO (0.2mL), DCE (0.5mL), 100°C, air, isolated yields.

As we observed 39% of methylthiolation product **4a** under metal-free conditions, we further screened the effect of solvents, temperature and other conditions to obtain the optimum yield of desired product **4a** (see Table S2, entry 10 in the supporting information).

Fig.1. OTREP diagram of the compound **4d**.

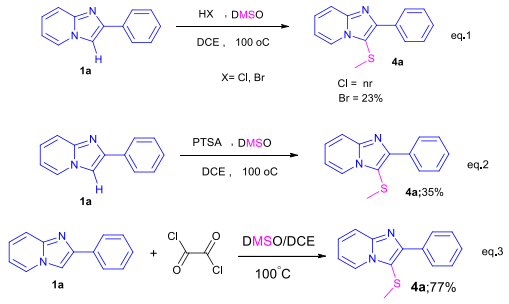
The best result was obtained using DMSO/DCE (0.2/0.5 mL) as solvent combination, 1.5 equivalents of **2a** (w.r.t. **1a**) as promoter,[32] in an open air, at 100 °C, 8 h reaction time. Under these optimized conditions (Table S2, entry 10), the reaction of unsubstituted imidazo[1, 2–a]pyridine **5** was subjected with DMSO **6**, the selective C-3 sulfenylated product **7** was isolated in 63% yield (Scheme 5, eq. 1). When C-3 substituted substrate 3-methylimidazo[1,2-a]pyridine **8** was subjected to the same reaction conditions, the formation desired product **9** was not observed (Scheme 5, eq. 2). These experiments (Scheme 5) indicate that, the regioselective sulfenylation of imidazo[1,2–a]pyridines occurs exclusively at C–3 position only, no reaction take place if the C–3 position is substituted by any other groups. Under the optimised conditions, different sulfonyl chlorides as promoter were studied for methylthiolation of **1a** (table 4). Among these, *p*-TsCl **2a** proved to be the best source to get the maximum yield of the desired product **4a**.

Table 5. Substrate scope of thiomethylation[a]



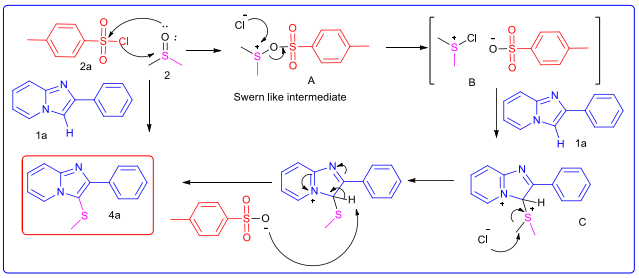
[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.375 mmol), DMSO **6** (0.2 mL), DCE(0.5 mL), air, 8.0 h, isolated yields.

After optimization of the conditions for the model reaction, the scope and limitation of this method for the methylthiolated imidazo[1, 2–a]pyridines **4** was studied (Table 5). The tandem methylthiolation of imidazo[1,2–a]pyridines with electron-donating (Me and SMe) and as well as partially withdrawing groups (Br, Cl and F) on the phenyl ring of phenylimidazo[1, 2–a]pyridines gave low to good yields (23–67%) of corresponding methylthiolated products **4b–4f**. One the structure of **4d** was further confirmed by single crystal XRD analysis (Figure 1).



Scheme 6. Control experiments

However, either strong electron donating or withdrawing groups failed to give the desired products **4g** and **4h**. With methyl and halogen (Br and Cl) substituents on either sides of phenyl ring gave moderate to good yields (40-63%) of corresponding methylthiolated products **4i–4o** including 52% yield of (E)-2-styrylimidazo[1,2–a]pyridine **4p**.



Scheme 7. Plausible Mechanism

Further, to ascertain the reaction mechanism of methylthiolations with DMSO, we performed some control experiments (Scheme 6). To understand the role of the halide, we have checked the reaction of **1a** with different hydro halides like HCl and HBr, in place of **2a** under the conditions studied, however no reaction was observed with HCl and 23% yield of **4a** was isolated with HBr (Scheme 6, eq. 1). The reaction of **1a** with PTSA and $(COCl)_2$ instead of **2a** under the optimization conditions, 35% and 77% of product **4a** was isolated (Scheme 6, eqs. 2 and 3). Based on the literature reports and control experiments a plausible reaction mechanism has been proposed (Scheme 7). Initially the reaction of **2a** with DMSO may generate Swern like intermediate **A**. Which may convert into intermediate **B**, and its subsequent reaction with **1a** leads the formation of imidazolium ion intermediate **C**. Finally, its oxidation will give the desired product **4a** with subsequent demethylation.[33]

Conclusions

In conclusion we revealed a novel and an efficient method for sulfenylation of imidazo[1, 2–a]pyridines using commercially available and environment-friendly sources of sulfenylating agents p-tosylchloride and DMSO. The method is pertinent to a wide range of imidazo[1,2–a]pyridines with good functional group tolerance and deliver good to excellent yields of sulfenylated products. The present strategy features an easy operational procedure under mild reaction conditions.

Experimental

All commercially available chemicals and reagents were used without any further purification unless otherwise indicated. ^{1}H and ^{13}C NMR spectra were recorded at 500, and 125 MHz, respectively. The spectra were recorded in $CDCl_3$ as solvent. Multiplicity was indicated as follows: s (singlet); d (doublet); t (triplet); m (multiplet); dd (doublet of doublets), etc. and coupling constants (J) were given in Hz. Chemical shifts are reported in ppm relative to TMS as an internal standard. The peaks around delta values of ^{1}H NMR (7.2), and ^{13}C NMR (77.0) are correspond to deuterated solvent chloroform respectively. Mass spectra were obtained using electron impact (EI)

ionization method. Progress of the reactions was monitored by thin layer chromatography (TLC). All products were purified through column chromatography using silica gel 100-200 mesh size using hexane/ethyl acetate as eluent unless otherwise indicated.

General procedure for thioarylation of imidazo[1,2–a]pyridines (3a)[23]

A clean washed boiling tube equipped with a magnetic stir bar was charged with 2-phenylimidazo[1,2–a]pyridine **1a** (0.0485 g, 0.25 mmol), 4-methylbenzene-1-sulfonyl chloride **2a** (0.0953 g, 0.75 mmol), CuI (0.00475 g, 0.025 mmol), Triphenyl phosphene (0.0965 g, 0.75 mmol) and toluene(2mL). The above mixture was stirred for 24h at 130°C in closedtube, and then the mixture was poured into 10 mL of saturated sodium bicarbonate solution. The product was extracted with Ethyl acetate (10 mL × 3) and dried with anhydrous Na_2SO_4. Removal of the solvent under reduced pressure, the left out residue was purified through column chromatography using silica gel (15% EtOAc/hexane) to get **3a** in 95 % yield (0.0753g).

2-Phenyl-3-(phenylthio)imidazo[1,2-a]pyridine (3aa)[34]

(Eluent: 20% EtOAc/hexane); White solid; 81% yield (60.9 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24-8.20(m, 3H), 7.72(d, *J* = 9.0 Hz, 1H), 7.42(t, *J* = 7.5 Hz, 2H), 7.35(t, *J* = 7.5 Hz, 1H), 7.29(t, *J* = 7.5 Hz, 1H), 7.18(t, *J* = 7.5 Hz, 2H), 7.10(t, *J* = 7.5 Hz, 1H), 6.99(d, *J* = 7.5 Hz, 2H), 6.81(t, *J* = 6.5 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ .159.3, 147.0, 135.0, 133.2, 129.43, 128.4, 128.3, 128.2, 126.5, 125.9, 125.4, 124.3, 117.5, 112.9, 106.1.

(4-Chlorophenyl)thio)-2-phenylimidazo[1,2-a]pyridine (3ab)[34]

(Eluent: 20% EtOAc/hexane); White solid; 90% yield(75.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24(d, *J* = 6.5 Hz, 1H), 8.19(d, *J* = 7.5 Hz, 2H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.44(t, *J* = 7.5 Hz, 2H), 7.39-7.33(m, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.93-6.87(m, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 147.1, 133.7, 133.1, 132.0, 129.5, 128.7, 128.4, 128.2, 126.7, 124.2, 117.7, 113.2, 105.6.

2-Phenyl-3-((4-(trifluoromethyl)phenyl)thio)imidazo[1,2-a]pyridine (3ac)

(Eluent: 20% EtOAc/hexane); White solid; m.p.: 162°C; 83% yield (76.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20(d, *J* = 6.5 Hz, 1H),8.16(d, *J* = 7.5 Hz, 1H), 7.75(d, *J* = 9.0 Hz, 1H), 7.42(t, *J* =8.5 Hz, 4H), 7.38-7.32(m, 2H), 7.05(d, *J* = 8.5 Hz, 2H), 6.87(t, *J* = 6.5 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 147.3, 140.4, 132.9, 129.7, 128.3, 127.0, 126.9, 126.2, 125.1, 124.9, 124.1, 117.7, 113.3, 104.4 . IR (KBr) 2940, 1630, 1601, 1496, 1269, 1229, 1165, 1082, 1011, 829, 693, 587. HRMS calcd for $C_{20}H_{14}N_2F_3S$: 371.0830, found: 371.0840.

3-((4-(Tert-butyl)phenyl)thio)-2-phenylimidazo[1,2-a]pyridine (3ad)

(Eluent: 20% EtOAc/hexane); White solid; m.p.: 139°C; 40% yield (36.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29(d, *J* = 6.5 Hz, 1H), 8.23(d, *J* = 7.5 Hz, 2H), 7.72(d, *J* = 9.0 Hz, 1H), 7.43(t, *J* = 7.5 Hz, 2H), 7.37-7.29(m, 2H), 7.22(d, *J* = 8.5 Hz, 2H),6.94(d, *J* = 8.5 Hz, 2H), 6.85(t, *J* = 6.5 Hz, 1H),1.23(s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 149.2, 146.9, 33.3, 131.5, 128.4, 128.3, 126.5, 126.4, 125.4, 124.5, 117.5, 112.9, 106.7, 34.3, 31.1. IR (KBr) 3023, 2960, 1629, 1490, 1348, 1268, 1232, 1113, 1008, 828, 746, 696, 547. HRMS calcd for $C_{23}H_{23}N_2S$: 359.1582, found: 359.1592.

3-([1,1'-Biphenyl]-4-ylthio)-2-phenylimidazo[1,2-a]pyridine (3ae)

(Eluent: 20% EtOAc/hexane); White solid; m.p.: 136 °C; 70% yield(65.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28(d, *J* = 7.0 Hz, 1H), 8.23(d, *J* = 7.5 Hz, 2H), 7.74(d, *J* = 9.0 Hz, 1H), 7.74-7.40(m, 6H), 7.42-7.36(m, 3H), 7.32-7.03(m, 2H), 7.05(d, *J* = 7.5 Hz, 2H), 6,84(t, *J* = 6.5 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 147.0, 139.9, 139.0, 134.1, 133.2, 128.7, 128.5, 128.38, 128.31, 128.0, 127.3, 126.7, 125.8, 124.4, 117.5, 113.0, 106.0. IR (KBr) 3028, 2254, 1629, 1473, 1339, 828, 698, 486. HRMS calcd for $C_{25}H_{19}N_2S$: 379.1269, found: 379.1288.

3-(Mesitylthio)-2-phenylimidazo[1,2-a]pyridine (3af)

(Eluent: 20% EtOAc/hexane); White solid; m.p.: 159 °C; 78% yield(67.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16(d, *J* = 7.5 Hz, 2H), 7.89(d, *J* = 7.0 Hz, 1H), 7.63(d, *J* = 9.0 Hz, 1H), 7.46(t, *J* = 7.5 Hz, 2H), 7.37(t, *J* = 7.5 Hz, 1H), 7.17(t, *J* = 8.5 Hz, 1H), 6.78(s, 2H), 6.72(t, *J* = 7.0 Hz, 1H), 2.19(s, 6H), 2.17(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 145.8, 140.2, 137.6, 132.9, 129.7, 128.7, 128.4, 128.0, 127.4, 126.8, 125.2, 124.2, 117.4, 112.5.109.1, 21.5, 20.7. IR (KBr) 3037, 2947, 1648, 1460, 1437, 1345, 1228, 1156, 1024, 846, 736, 580. HRMS calcd for $C_{22}H_{21}N_2S$: 345.1425, found: 345.1428.

3-(Naphthalen-1-ylthio)-2-phenylimidazo[1,2-a]pyridine (3ag)[34]

(Eluent: 20% EtOAc/hexane); White solid; 82% yield(72.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24(t, *J* = 7.0 Hz, 3H), 7.75(d, *J* = 9.0 Hz, 2H), 7.70(t, *J* = 6.5 Hz, 1H), 7.68(d, *J* = 8.5 Hz, 1H), 7.55(t, *J* = 6.5 Hz, 1H), 7.43-7.39(m, 2H), 7.38-7.34(m, 4H), 7.30(t, *J* = 7.5 Hz, 1H), 7.15-7.13(m, 1H). 6.79(t, *J* = 6.5 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 147.1, 133.2, 132.4, 131.7, 129.1, 128.7, 125.3, 128.38, 123.30, 127.6, 126.9, 126.7, 126.6, 125.6, 124.4, 123.7, 123.3, 117.5, 113.0, 106.0.

2-Phenyl-3-(p-tolylthio)imidazo[1,2-a]pyridine (3a)[23]

(Eluent: 20% EtOAc/hexane); White solid; 95% yield(75.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16(d, *J* = 7.0 Hz, 1H), 8.13(d, *J* = 7.0 Hz, 2H) 7.63(d, *J* = 8.5 Hz, 2H), 7.33(t, *J* = 7.5 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 6.91(d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.73 (t, *J* = 6.5 Hz, 1H) 2.14(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 146.9, 135.9, 133.3, 131.4, 130.1, 128.4, 128.3, 126.4, 125.7, 124.4, 117.5, 112.9, 106.7, 20.7.

8-methyl-2-phenyl-3-(p-tolylthio)imidazo[1,2-a]pyridine (3b)[23]

(Eluent: 20% EtOAc/hexane); White solid; 95% yield (78.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19(d, *J* = 7.5 Hz, 2H), 8.14(d, *J* = 7.0 Hz, 1H), 7.47(s, 1H), 7.42(t, *J* = 7.5 Hz, 2H), 7.35(d, *J* = 7.5 Hz, 1H), 7.02(d, *J* = 8.0 Hz, 2H), 6.90(d, *J* = 7.0 Hz, 2H), 6.68(d, *J* = 6.5 Hz, 1H), 2.42(s, 3H), 2.25(s,3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 147.4, 137.7, 135.8, 133.5, 131.8, 130.1, 128.3, 128.2, 125.6, 123.6, 116., 115.5, 105.9, 101.6, 21.3, 20.8.

6-Methyl-2-phenyl-3-(p-tolylthio)imidazo[1,2-a]pyridine (3c)[22]

(Eluent: 20% EtOAc/hexane); White solid; 81% yield (67.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19(d, *J* = 7.5Hz, 2H), 8.07(s, 1H), 7.53(d, *J* = 7.0 Hz, 2H), 7.41(t, *J* =8.0 Hz, 2H), 7.18(d, *J* = 9.0 Hz, 1H), 7.03(d, *J* = 8.0 Hz, 2H), 6.91(d, *J* = 8.5 Hz, 2H), 2.31(s, 3H), 2.26(s.3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 146.6, 135.8, 133.5, 131.8, 130.1, 129.6, 128.3, 128.2, 125.7, 125.5, 122.28, 122.2, 116.9, 106.1, 103.7, 20.8, 18.3.

6-Chloro-2-phenyl-3-(p-tolylthio)imidazo[1,2-a]pyridine (3d)

(Eluent: 20% EtOAc/hexane); White solid; m.p.: 166 °C; 98% yield(86.2 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, H), 8.20 (d, *J* = 7.0 Hz, 2H), 7.65 (d, *J* = 9.5 Hz, 1H), 7.43 (t, *J* = 7.0 Hz, 2H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.27-7,25(m, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.90(d, *J* = 8.5 Hz, 2H), 2.26 (s, 3H), 13C NMR (125 MHz, CDCl3) δ 151.8, 145.2, 146,3, 132.9, 130.8, 130.2, 128.7, 128.4, 1282. 127.9, 125.9, 122.4, 121.4, 117.9, 107.7, 20.8. IR (KBr) 3427, 2921, 2373, 1439, 1327, 1077, 796, 692, 485. HRMS calcd for $C_{21}H_{18}N_2ClS$: 365.0879, found: 365.0846.

6-Bromo-2-phenyl-3-(p-tolylthio)imidazo[1,2-a]pyridine (3e)[22]

(Eluent: 20% EtOAc/hexane); White solid; 95% yield(93.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41(s, 1H), 8.20 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 9.0 Hz, 1H), 7.43 (t, *J* = 7.0 Hz, 2H), 7.39-7.35 (m, 2H), 7.04 (d, *J* = 7.5 Hz, 2H), 6.91 (d, *J* = 8.0Hz, 2H), 2.26 (s, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 145.3, 136.3, 132.8, 130.8, 130.2, 130.0, 128.7, 128.4, 128.2, 125.8, 124.6, 118.8, 107.9, 107.6, 20.8.

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6-Bromo-8-methyl-2-phenyl-3-(p-tolylthio)imidazo[1,2-a]pyridine (3f)

(Eluent: 20% EtOAc/hexane); liquid; 64% yield(65.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29(s, 1H), 8.19 (d, *J* = 7.5 Hz, 2H), 7.43-7.36(m, 3H), 7.19(s, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 2.69(, 3H), 2.26(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.8, 136.1, 131.2, 130.4, 130.2, 129.0, 128.8, 128.7, 128.5, 128.4, 125.8, 122.4, 107.79, 107.75, 20.8, 16.6. IR (Nujol) 3429, 2916, 1600, 1485, 1437, 1338, 1079, 805, 693, 486. HRMS calcd for $C_{21}H_{18}N_2SBr$: 409.0374, found: 409.0379.

2-(4-(Methylthio)phenyl)-3-(p-tolylthio)imidazo[1,2-a]pyridine (3g)

(Eluent: 20% EtOAc/hexane); White solid; m.p.: 126 °C; 72% yield(65.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25(d, *J* = 7.5 Hz, 1H), 8.18(d, *J* = 8.5 Hz, 2H), 7.70(d, *J* = 6.0 Hz, 1H), 7.30(d, *J* = 6.5 Hz, 3H), 7.00(d, *J* = 8.0 Hz, 2H), 6.90(d, *J* = 8.5 Hz, 2H), 6.82(t, *J* = 6.5 Hz, 1H), 2.48(s,3H0, 2.23(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.5, 146.9, 139.1, 135.9, 131.3, 130.1, 130.0, 128.5, 126.5, 126.0, 125.7, 124.3, 117.3, 112.8, 106.4, 20.7, 15.4. IR (KBr) 2917, 1597, 1459, 1339, 1094, 801, 728, 483. HRMS calcd for $C_{21}H_{19}N_2S_2$: 363.0990, found: 363.0983.

2-(2-Fluorophenyl)-3-(p-tolylthio)imidazo[1,2-a]pyridine (3h)

(Eluent: 20% EtOAc/hexane); liquid; 89% yield(74.2 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18(d, J = 6.5 Hz, 1H), 7.74-7.61(m, 2H), 7.42-7.28(m, 2H), 7.23-7.14(m, 2H), 6.99(d, J = 8.0 Hz, 2H), 6.86-6.82(m, 3H), 2.22(s, 3H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6 (d, *J* = 72.5 Hz), 135.8,131.9, 131., 130.3(d, *J* = 7.6 Hz), 129.9, 126.3, 125,9, 124.5, 123.8, 121.6 (d, *J* = 14.0 Hz), 117.7, 116.0(d, *J* = 22.5 Hz), 113.0, 109.4, 20.7. IR (Nujol) 3401, 2923, 1892, 1631, 1489, 1342, 1222, 1099, 803, 757, 483. HRMS calcd for $C_{20}H_{16}N_2FS$: 335.1018, found: 335.1013.

2-(4-Chlorophenyl)-3-(p-tolylthio)imidazo[1,2-a]pyridine (3i)[22]

(Eluent: 20% EtOAc/hexane); White solid; 92% yield(81.2 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26(d, *J* = 7.0 Hz, 1H), 8.19(d, *J* = 8.5 Hz, 2H), 7.70(d, *J* = 9.0 Hz, 1H), 7.39 (d, *J* = 9.0 Hz, 2H), 7.30(t, *J* = 7.5 Hz, 1H), 7.01(d, *J* = 8.0 Hz, 2H),6.88-6.66(m, 3H), 2.23(s, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 146.9, 136.1, 134.4, 131.8, 131.0, 130.1, 129.9, 128.5, 126.7, 125.7, 124.4, 117.5, 113.0, 107.0, 20.8.

2-(4-Bromophenyl)-3-(p-tolylthio)imidazo[1,2-a]pyridine (3j)

Eluent: 20% EtOAc/hexane); White solid; m.p.: 131 °C; 79% yield (80.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16(d, *J* = 6.5 Hz, 1H), 8.01(d, *J* = 8.0 Hz, 2H), 7.61(d, *J* = 9.0 Hz, 1H), 7.44(d, *J* = 8.5 Hz, 2H), 7.21(t, *J* = 8.0 Hz, 1H), 6.91(d, *J* = 8.0 Hz, 2H), 6.78-6.73(m, 3H), 2.13(s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 146.9, 136.1, 132.2, 131.4, 131.0, 130.1, 129.7, 126.7, 125.7, 124.4, 123.1, 122.8, 122.2, 17.5, 113.1, 107.0, 20.8. IR (KBr) 3029, 2859, 1629, 1480, 1382, 1230, 1081, 800, 669, 479. HRMS calcd for $C_{20}H_{16}N_2SBr$: 343.1269, found: 343.1254.

2-(4-Methoxyphenyl)-3-(p-tolylthio)imidazo[1,2-a]pyridine (3k)[23]

(Eluent: 20% EtOAc/hexane); White solid; 54% yield(47.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09(d, *J* = 6.5 Hz, 1H), 7.67(d, *J* = 6.5 Hz, 1H), 7.23(t, *J* = 8.0 Hz, 1H), 7.09(t, *J* = 7.5 Hz, 2H), 7.01(t, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.82(s, 2H), 6.79-6.75(m, 2H), 3.62(s, 3H), 3.51(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 151.6, 150.1, 149.9, 146.9, 135.6, 129.0, 126.0, 125.0, 124.3, 123.2, 117.7, 116.6, 115.6, 112.9, 112.2, 108.8, 55.7, 55.6.

2-(2,6-Dimethoxyphenyl)-3-(p-tolylthio)imidazo[1,2-a]pyridine (3l)

(Eluent: 20% EtOAc/hexane); White solid; m.p.: 141 °C; 99% yield(93.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16(d, *J* = 7.0 Hz, 1H), 7.74(d, *J* = 9.0 Hz, 1H), 7.28(t, *J* = 8.0 Hz, 1H), 7.11(s, 1H), 6.99(d, *J* = 8.5 Hz, 2H), 6.90(s, 2H), 6.87(d, *J* = 8.0 Hz, 2H), 6,82(t, *J* = 6.5 Hz, 1H), 3.709(s, 3H), 3.62(s, 3H), 223(s,3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 151.5, 149.8, 146.7, 135.4, 131.7, 129.7, 125.7, 124.3, 123.2, 117.6, 116.7, 115.5, 112.8, 112.1, 109.3, 55.7, 55.5, 20.7. IR (KBr) 2955, 2831, 1630, 1490, 1223, 1040, 807, 744, 425. HRMS calcd for $C_{22}H_{21}N_2O_2S$: 377.1324, found: 377.1328.

4-(3-(p-Tolylthio)imidazo[1,2-a]pyridin-2-yl)benzonitrile (3m)[23]

(Eluent: 20% EtOAc/hexane); White solid; 79% yield(67.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39(d, *J* = 8.5 Hz, 2H),8.29(d, *J* = 7.0 Hz, 1H), 7.72-7.68(m, 3H), 7.35(t, *J* = 8.5 Hz, 1H),7.03(d, *J* = 8.0 Hz, 2H),6.91-6.87(m, 3H), 2.24(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4, 146.9, 137.8, 136.4, 132.0, 130.5, 130.2, 128.5, 127.0, 125.8, 124.4, 118.8, 117.7, 113.4, 111.5, 108.3, 20.7.

4-(8-Methyl-3-(p-tolylthio)imidazo[1,2-a]pyridin-2-yl)benzonitrile (3n)

(Eluent: 20% EtOAc/hexane); White solid; m.p.: 162 °C; 72% yield (82.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.0 Hz, 2H), 8.06 (d, *J* = 7.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.04(d, *J* = 7.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 2H), 6.70 (t, *J* = 7.0 Hz, 1H) 2.59 (s, 3H), 2.15(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 1477.2, 138.0, 136.1, 131.8, 130.7, 130.1, 128.5, 127.7, 125.6, 122.1, 118.9, 113.3, 111.2, 108.4, 20.6, 16.5. IR (KBr) 2921, 2218, 1603, 1488, 1348, 1248, 845, 813, 747, 550, 505. HRMS calcd for $C_{22}H_{18}N_3S$: 356.1221, found: 356.1209.

4-(7-Methyl-3-(p-tolylthio)imidazo[1,2-a]pyridin-2-yl)benzonitrile (3o)

(Eluent: 20% EtOAc/hexane); White solid; m.p.: 201 °C; 60% yield(53.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.0 Hz, 2H), 7.98(s, 1H), 7.57 (d, *J* = 7.0 Hz, 2H), 7.52(d, *J* = 9.0 Hz, 1H), 7.11(d, *J* = 9.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 2H),6.79 (d, *J* = 8.0 Hz, 2H), 2.22 (s, 3H), 2.15(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 146.0, 137.9, 136.2, 131.9, 130.8, 130.2, 128.4, 125.5, 123.4, 122.0, 118.8, 117.0, 111.4, 107.7, 20.7, 18.2. IR (KBr) 2920, 2219, 1605, 1492, 1464, 1334, 856, 801, 555, 477. HRMS calcd for $C_{22}H_{18}N_3S$: 356.1221, found: 356.1209.

2-(8-Methyl-3-(p-tolylthio)imidazo[1,2-a]pyridin-2-yl)benzonitrile (3p)

(Eluent: 20% EtOAc/hexane); White solid; m.p.: 162 °C; 74% yield(66.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58(s, 1H), 8.50 (d, *J* = 8.0 Hz, 1H), 8.17 (d, *J* = 6.5 Hz, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.51(t, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 6.5 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.81(t, *J* = 7.0 Hz, 1H), 2.70(s, 3H), 2.26 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8. 147.3, 136.2, 135.0, 132.4, 131.8, 131.4, 130.2, 127.8, 125.8, 122.2, 118.8, 113.4, 112.4, 108.0, 20.7, 16.6. IR (KBr) 2920, 2218, 1608, 1488, 1348, 1248, 845, 812, 747, 550, 505. HRMS calcd for $C_{22}H_{18}N_3S$: 356.1221, found: 356.1209.

2-(Thiophen-2-yl)-3-(p-tolylthio)imidazo[1,2-a]pyridine (3q)

(Eluent: 20% EtOAc/hexane); White solid; m.p.: 210 °C; 65% yield(52.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25(d, *J* = 7.0 Hz, 1H), 8.00(d, *J* = 3.5 Hz, 1H), 7.68(d, *J* = 9.0 Hz, 1H),7.36(d, *J* = 5.0 Hz, 1H), 7.28(t, *J* = 9.0 Hz, 1H), 7.09(t, *J* = 4.0 Hz, 1H),7.00(d, *J* = 8.5 Hz, 2H), 6.96(d, *J* = 8.0 Hz, 2H), 6.81(t, *J* = 6.0 Hz, 1H), 2.23(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8, 146.4, 136.2, 136.1, 130.8, 13.00, 127.6, 126.6, 126.4, 126.1, 124.2, 117.2, 112.9, 106.0, 20.7. IR (KBr) 3043, 2918, 1630, 1488, 1339, 748, 687, 483. HRMS calcd for $C_{18}H_{15}N_2S_2$: 323.0677, found: 323.0696.

(E)-2-Styryl-3-(p-tolylthio)imidazo[1,2-a]pyridine (3r)

Eluent: 20% EtOAc/hexane); White solid; m.p.: 170 °C; 85% yield(73.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18(d, *J* = 7.0 Hz, 1H), 7.83(d, *J* = 16.0 Hz, 1H), 7.66-7.60(m, 3H), 7.50(d, *J* = 16.0 Hz, 1H), 7.35(t, *J* = 7.5 Hz, 2H), 7.29-7.24(m, 2H), 7.01(d, *J* = 8.0 Hz, 2H), 6.95(d, *J* = 8.5 Hz, 2H), 6.78 (t, *J* = 6.5 Hz, 1H), 2.24(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 147.4, 136.9, 136.2, 132.6, 131.2, 130.0, 128.5, 127.9, 126.8, 126.5, 124.2, 118.2, 117.7, 112.5, 109.6, 20.7. IR (KBr) 3032, 2921, 1631, 1443, 1339, 1231, 921, 731, 680, 482. HRMS calcd for

$C_{22}H_{19}N_2S$: 343.1269, found: 343.1254.

2-Phenyl-3-(p-tolylthio)benzo[d]imidazo[2,1-b]thiazole (3s)[23]

Eluent: 20% EtOAc/hexane); White solid; 52% yield(48.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26-8.21((m, 1H),7.92-7.89(m, 2H), 7.57(t, J = 5.0 Hz, 1H), 7.50(d, J = 16.0 Hz, 1H), 6.98-6.94(m, 2H), 2.28(s,3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ138.1,138.0, 136.5, 135.9, 133.4, 132.9, 131.6,130.0,129.5,129.3,129.0,128.1,128.0,127.9,127.7,126.2,126.0 ,125.4,124.3,123.8,114.2,21.2.

General procedure for thiomethylation of imidazo[1,2-a]pyridines (4a)[31]

A clean washed boilingtube equipped with a magnetic stir bar was charged with 2-phenylimidazo[1,2-a]pyridine **1a** (0.0485 g, 0.25 mmol), 4-methylbenzene-1-sulfonyl chloride **2a** (0.0733 g, 0.375 mmol) , Dimethyl sulphoxide(0.2 mL) and Dichloroethane (0.5 mL). The above mixture was stirred for 8h to open air at 100°C, and then the mixture was poured into 10 mL of saturated sodium bicarbonate solution. The product was extracted with Ethyl acetate (10 mL × 3) and dried with anhydrous Na_2SO_4. Removal of the solvent under reduced pressure, the left out residue was purified through column chromatography using silica gel (15% EtOAc/hexane) to get 4a in 91 % yield (0.054g), white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, J = 8.0 Hz, 1H), 8.29 (d, J = 7.5 Hz, 2H), 7.66 (d, J = 9.0 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.38 (t, J = 7.5 Hz, 1H), 7.27 (t, J = 7.5 Hz, 1H), 6.91 (t, J = 6.5 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7, 146.2, 133.7, 128.2, 128.1, 125.8, 124.1, 117.5, 112.6, 18.0. HRMS calcd for $C_{14}H_{13}N_2S$: 241.0788, found: 241.0788.

3-(Methylthio)-2-(p-tolyl)imidazo[1,2-a]pyridine (4b)

(Eluent: 20% EtOAc/hexane); White solid; m.p.: 102 °C; 42% yield (26.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49(d, *J* = 6.5 Hz, 1H), 8.18(d, *J* = 7.5 Hz, 2H), 7.67(d, *J* = 9.0 Hz, 1H), 7.30-7.26(m, 4H), 6.93(t, *J* = 6.5 Hz, 1H), 2.41(s, 3H), 2.26(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 146.2, 138.1, 130.8, 129.1, 128.1, 125.8, 124.1, 117.4, 116.2, 112.6, 111.0, 29.6, 21.3. HRMS calcd for $C_{15}H_{15}N_2S$: 255.0946, found: 255.0956.

3-(Methylthio)-2-(4-(methylthio)phenyl)imidazo[1,2-a]pyridine (4c)

(Eluent: 20% EtOAc/hexane); liquid; 23% yield (16.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48(d, *J* = 6.5 Hz, 1H), 8.25(d, *J* = 8.0 Hz, 2H), 7.36(d, *J* = 7.5 Hz, 2H), 7.29(t, *J* = 7.0 Hz, 1H), 6.94(t, *J* = 7.0 Hz, 1H), 2.54(s, 3H), 2.26(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 146.2, 138.7, 128.4, 126.1, 125.9, 124.1, 117.4, 112.7, 18.1, 15.5. IR (Nujol) 3400, 2922, 2316, 1649, 1458, 1344, 1094, 824, 757, 690. HRMS calcd for $C_{15}H_{15}N_2S_2$: 287.0677, found: 287.0679.

2-(4-Chlorophenyl)-3-(methylthio)imidazo[1,2-a]pyridine (4d)

(Eluent: 20% EtOAc/hexane); White solid; m.p.: 95 °C; 51% yield (34.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46(d, *J* = 8.5 Hz, 3H), 7.66(d, *J* = 7.5 Hz, 1H), 7.43(s, 2H), 7.29(t, *J* = 7.5 Hz, 1H), 6.94(d, *J* = 6.0 Hz, 1H), 2.25(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5, 146.3, 134.1, 132., 129.4, 128.5, 126.1, 124.2, 117.6, 112.8, 111.4, 18.0. IR (KBr) 2918, 2370, 1698, 1462, 1340, 1089, 842, 732, 551. HRMS calcd for $C_{14}H_{12}N_2SCl$: 275.0410, found: 275.0415.

2-(2-Fluorophenyl)-3-(methylthio)imidazo[1,2-a]pyridine (4e)

Eluent: 20% EtOAc/hexane); White solid; m.p.: 110 °C; 67% yield (42.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37(d, *J* = 6.5 Hz, 1H), 7.622 -> 7.62 (m, 2H), 7.35-7.30(m, 1H), 7.23(t, *J* = 7.0 Hz, 1H), 7.18(t, *J* = 7.0 Hz, 1H), 7.12(t, *J* = 9.0 Hz, 1H), 6.88(t, *J* = 7.0 Hz, 1H), 2.16(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1(d, *J* = 248 Hz), 146.5, 145.5, 132.0, 130.1(d, *J* = 8.0 Hz), 125.7, 124.1, 123.9, 122.0(d, *J* = 14.0 Hz), 117.8, 115.9 (d, *J* = 22.0 Hz), 113.7, 112.8, 17.7. IR (KBr) 2925, 1719, 1630, 1478, 1344, 1222, 1099, 968, 799, 759. HRMS calcd for $C_{14}H_{12}N_2SF$: 259.0705, found: 259.0715.

2-(4-Bromophenyl)-3-(methylthio)imidazo[1,2-a]pyridine (4f)

Eluent: 20% EtOAc/hexane); White solid; m.p.: 109 °C; 41% yield (32.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48(d, *J* = 6.5 Hz, 1H), 8.19(d, *J* = 8.6 Hz, 2H), 7.68(d, *J* = 8.5 Hz, 1H), 7.61(d, *J* = 8.5 Hz, 2H), 7.31(t, *J* = 8.0 Hz, 1H), 6.96(t, *J* = 6.5 Hz, 1H), 2.25(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 147.7, 132.9, 131.2, 127.7, 125.6, 119.0, 114.4, 19.5. IR (KBr) 3370, 2922, 2372, 1650, 1493, 1227, 827, 728, 699, 508. HRMS calcd for $C_{14}H_{12}N_2SBr$: 318.9905, found: 318.9911.

8-Methyl-3-(methylthio)-2-phenylimidazo[1,2-a]pyridine (4i)

(Eluent: 20% EtOAc/hexane); White solid; m.p.: 102 °C; 51% yield(32.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28(d, *J* = 6.5 Hz, 1H), 8.18(d, *J* = 7.0 Hz, 2H), 7.40(t, *J* = 7.5 Hz, 2H), 7.30(t, *J* = 7.5 Hz, 1H), 7.01(d, *J* = 7.0 Hz, 1H), 6.78(t, *J* = 7.0 Hz, 1H), 2.59 (s, 3H), 2.17(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 146.6, 134.0, 128.4, 128.3, 128.0, 127.6, 124.7, 122.0, 116.1, 112.7, 111.6, 29.6, 18.2. IR (KBr) 2922, 1732, 1468, 1255, 1071, 743, 699. HRMS calcd. for $C_{15}H_{15}N_2S$: 255.0956, found: 255.0956.

2-(4-Chlorophenyl)-6-methyl-3-(methylthio)imidazo[1,2-a]pyridine (4j)

(Eluent: 20% EtOAc/hexane); liquid; m.p.: 152 °C 63% yield(45.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17(d, *J* = 8.5 Hz, 3H), 7.47(d, *J* = 9.0 Hz, 1H), 7.35(d, *J* = 8.0 Hz, 2H), 7.07(d, *J* = 8.5 Hz, 1H), 2.32(s, 3H), 2.16(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 1487.3, 145.3, 1333.9, 132.4, 129.2, 129.1, 128.4, 122.6, 121.9, 116.8, 110.9, 18.3, 18.1. IR (Nujol) 2919, 1647, 1490, 1404, 1330, 1085, 1008, 841, 726. HRMS calcd for $C_{15}H_{14}N_2SCl$: 289.0566, found: 289.0576.

2-(2-Chlorophenyl)-8-methyl-3-(methylthio)imidazo[1,2-a]pyridine (4k)

(Eluent: 20% EtOAc/hexane); liquid; 60% yield (43.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32(d, *J* = 6.5 Hz, 1H), 7.67(t, *J* = 7.5 Hz, 1H), 7.41-7.37(m, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.18(t, *J* = 8.5 Hz, 1H), 7.11(d, *J* = 7.0 Hz, 1H), 6.87 (t, *J* = 7.0 Hz, 1H), 2.66(s, 3H), 2.22(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 159.2, 146.9, 145.1, 132.3, 130.06, 130.00, 127.8, 124.6, 123.9, 123.3, 120.0, 115.8, 115.7, 114.0, 112.8, 17.8, 16.8. IR (Nujol) 2923, 1625, 1483, 1354, 1221, 1096, 764, 546. HRMS calcd for $C_{15}H_{14}N_2SCl$: 289.0566, found: 289.0569.

6-Methyl-3-(methylthio)-2-phenylimidazo[1,2-a]pyridine (4l)

(Eluent: 20% EtOAc/hexane); White solid; m.p.: 121 °C; 40% yield(25.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28(d, *J* = 7.0 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.35 (s, 1H), 7.30(t, *J* = 7.0 Hz, 1H), 6.70 (d, *J* = 7.0 Hz, 1H), 2.36(s, 3H), 2.17(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 146.7, 142.3, 137.7, 133.8, 128.3, 128.19, 128.12, 123.4, 116.2, 116.0, 115.3, 110.6, 29.6, 21.3. IR (KBr) 2920, 2369, 1638, 1489, 1352, 1263, 776, 672. HRMS calcd for $C_{15}H_{15}N_2S$:255.0956, found: 255.0938.

6-Bromo-8-methyl-3-(methylthio)-2-phenylimidazo[1,2-a]pyridine (4m)

(Eluent: 20% EtOAc/hexane); yellow solid; m.p.: 132 °C; 43% yield (35.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.26(d, *J* = 7.0 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.38(t, *J* = 7.5 Hz, 1H), 7.17(s, 1H), 2.65(s, 3H), 2.25(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.8, 145.0, 133.6, 128.7, 128.3, 128.0, 122.2, 112.2, 107.5, 18.2, 16.6. IR (KBr) 2919, 2372, 1648, 1474, 1398, 968, 776, 694, 691. HRMS calcd for $C_{15}H_{14}N_2SBr$: 343.1269, found: 343.1254.

6-Chloro-2-(2-fluorophenyl)-3-(methylthio)imidazo[1,2-a]pyridine (4n)

(Eluent: 20% EtOAc/hexane); White solid; m.p.: 115 °C; 45% yield (33.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48(s, 1H), 7.58(t, *J* = 7.0 Hz, 1H), 7.64(d, *J* = 9.5 Hz, 1H),7.43-7.39(m, 1H), 7.29-7.18(m, 3H), 2.25(s, 3H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1(d, *J* = 248 Hz), 146.5, 144.8, 131.9, 130.4(d, *J* = 7.0 Hz), 127.2, 124.0, 122.2, 121.6(d, *J* = 17.5 Hz), 118.3, 116.0 (d, *J* = 22.0 Hz), 114.6, 17.8. IR (KBr) 2925, 1474,

1325, 1218, 1073, 806, 755, 668, 456. HRMS calcd for $C_{14}H_{11}N_2FSCl$: 293.0316, found: 293.0310.

3-(Methylthio)-2,6-diphenylimidazo[1,2-a]pyridine (4o)

Eluent: (50% EtOAc/hexane); White solid; m.p.: 186 °C; 61% yield(48.2 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57(s, 1H), 8.24(d, *J* = 7.0 Hz, 2H), 7.65(d, *J* = 9.5 Hz, 1H), 7.56(d, *J* = 7.0 Hz, 2H), 7.7.50-7.39(m, 5H), 7.36-7.31(m, 2H), 2.20(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 145.6, 137.3, 133.7, 129.1, 128.5, 128.3, 128.2, 1281, 127.7, 127.1, 126.9, 126.7, 126.5, 121.4, 117.4, 11.7, 18.2. IR (KBr) 3056, 2964, 1335, 1261, 1094, 1021, 804, 762, 693, 513. HRMS calcd for $C_{20}H_{17}N_2S$: 317.1112, found: 317.1111.

(E)-3-(Methylthio)-2-styrylimidazo[1,2-a]pyridine (4p)

Eluent: (30% EtOAc/hexane); liquid; 52% yield(34.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31(d, *J* = 6.5 Hz, 1H),7.67(d, *J* = 16.0 Hz, 1H) 7.55(t, *J* = 8.0 Hz, 3H), 7.42(d, *J* = 16.5 Hz, 1H), 7.30(t, *J* = 7.5 Hz, 2H), 7.22-7.199m, 2H), 6.81(t, *J* = 6.5 Hz, 1H), 2.20(s, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0. 146.9, 1371, 131.8, 128.6, 127.8, 126.8, 126.3, 124.0, 118.4, 117.2, 113.8, 112.4, 18.7. IR (Nujol) 3399, 2921, 1634, 1496, 1344, 1263, 1074, 969, 758, 451. HRMS calcd for $C_{16}H_{15}N_2S$: 267.0956, found: 267.0969.

3-(Methylthio)imidazo[1,2-a]pyridine (7)

Eluent: (30% EtOAc/hexane); liquid; 63% yield(24.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, *J* = 7.0 Hz, 1H), 7.77(s, 1H), 7.65(d, *J* = 9.0 Hz, 1H), 7.26(t, *J* = 8.0 Hz, 1H), 6.93(t, *J* = 7.0 Hz, 1H), 2.27(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 1140.0, 125.2, 123.9, 118.0, 112.7, 29.6. IR (Nujol) 2923, 2853, 1648, 1462, 1093, 805, 759. HRMS calcd for $C_8H_9N_2S$: 165.0486, found: 165.0487.

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Notes and references

1. F. Couty, G. Evano, in: Comprehensive Heterocyclic Chemistry III, (eds.: Katritzky A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor R. J. K.), *Elsevier*, *Oxford*, 2008, **11**, 409.
2. J. Liu, Q. Chen, *Huaxue Jinzhan*, 2010, **22**, 631.
3. C. A. E. Gueiffier Gueiffier *Mini-Rev. Med. Chem*. 2007, **7**, 888.
4. G. Bartholini, *L.E.R.S. Monograph Series,* 1993, **8**, 1.
5. E. Abignente, de. Actualites *Chimie Therapeutique*, 1991, **18**, 193.
6. S. Z. Langer, S. Arbilla, J. Benavides, B. Scatton, *Adv. Biochem. Psychopharmacol*, 1990, **46**, 61.
7. K. Mizushige, T. Ueda, K. Yukiiri, H. Suzuki, *Cardiovasc. Drugs Rev.* 2002, **20**, 163.
8. L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Biancotti, A. Gamba, W. J. Murmann, *Med. Chem.* 1965, **8**, 305.
9. Boerner, R. J. Moller, H. J. *Psychopharmakother,* 1997, **4**, 145.
10. K. Gudmundsson and S. D. Boggs. *PCT Int. Appl*.WO 2006026703, 2006.
11. 11. S. Liu, H. Xi, J. Zhang, X. Wu, Q. Gao, A. Wu, *Org. Biomol. Chem.* 2015, **13**, 8807- 8811.
12. V. B. Kurteva, L. A. Lubenov, D. V. Antonova, *RSC Adv*. 2014, **4**, 175.
13. X. Xiao, Y. Xie, S. Bai, Y. Deng, H. Jiang, W. Zeng, *Org. Lett*. 2015, **17**, 3998.
14. D. C. Mohan, S. N. Rao, S. Adimurthy, *J. Org. Chem*. 2013, **78**, 1266.
15. D. R. Reddy, P. Venkatanarayana, N.N.K.Reddy, D. Bairagi, S. Adimurthy, *J. Org.Chem.* 2014, **79**, 11277.
16. D. C. Mohan, S. N. Rao, C. Ravi. S. Adimurthy, *Asian J. Org. Chem.* 2014, **3**, 609.
17. G. J. Mukund, M. Shelke, Cameron, T. S. Kumar, A. *J. Org. Chem.* 2015, **80**, 5272.
18. Q. Wu, D. Zhao, X. Qin, J. Lan, J. You, Chem. Commun., 2011, 47, 9188.
19. H. Cao, H. Zhan, Y. Lin, X. Lin, Z. Du, H. Jiang, *Org. Lett.* 2012, **14**, 7.
20. C. Ravi, D. C. Mohan, S. Adimurthy, *Org. Lett*. 2014, **16**, 2978.
21. Yan, S. Y. Liu, B. Liu, Y.Liu, B.F. Shi, *Chem. Commun*. 2015, **51**, 4069.
22. M. Hiebel, S. B. Raboin, *Green Chem*. 2015, **17**, 937.
23. A. K. Bagdi, S. Mitra, M. Ghosh, A. Hajra, *Org. Biomol. Chem.* 2015, **13**, 3314.
24. When we screened different solvents like polar and nonpolar, reactions were not efficient and produced traces amounts of product 3a (see Table S1, supporting information).
25. C. Shen, P. Zhang, Q. Sun, S. Bai, T. S. A. Hor, X. Liu, *Chem. Soc. Rev*. 2015, **44**, 291.
26. C. Zhang, N. Jiao, *J. Am. Chem. Soc.* 2010, **132**, 28.
27. A. E. King, T. C. Brunold, S. S. Stahl, *J. Am. Chem. Soc.* 2009, **131**, 5044.
28. O. Basl, C.-J. Li, *Chem. Commun*. 2009, 4124.
29. P. Sharma, S. Rohilla, N. Jain, J. Org. Chem. 2015, **80**, 4116.
30. C. Dai, Z. Xu, F. Huang, Z. Yu, Y. Gao, *J. Org. Chem*. 2012, **77**, 4414.
31. S. M. Patila, S. Kulkarni, M. Mascarenhas, R. Sharma, S. M. Roopan, A. Roychowdhury, *Tetrahedron*, 2013, **69**, 8255.
32. After screening of different sulfonyl chlorides as promoters, 4-methylbenzene-1-sulfonyl chloride 2a was found to be the best for this transformation (see Table S3, ESI).
33. W. Zhao, P. Xie, Z. Bian, A. Zhou, H. Ge, M. Zhang, Y. Ding, L. Zheng, J. Org. Chem. 2015, **80**, 9167−9175.
34. W. Ge, X. Zhu, Y. Wei, *Eur. J. Org. Chem.* 2013, 6015.