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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201601431

Link to VoR: http://dx.doi.org/10.1002/adsc.201601431

10.1002/adsc.201601431

COMMUNICATION

DOI: 10.1002/adsc.201

One-pot Three-component Synthesis of Alkyl/Arylthioether-Substituted Imidazo[1,2-α]pyridine Derivatives via C(sp^2)-H Functionalization

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201

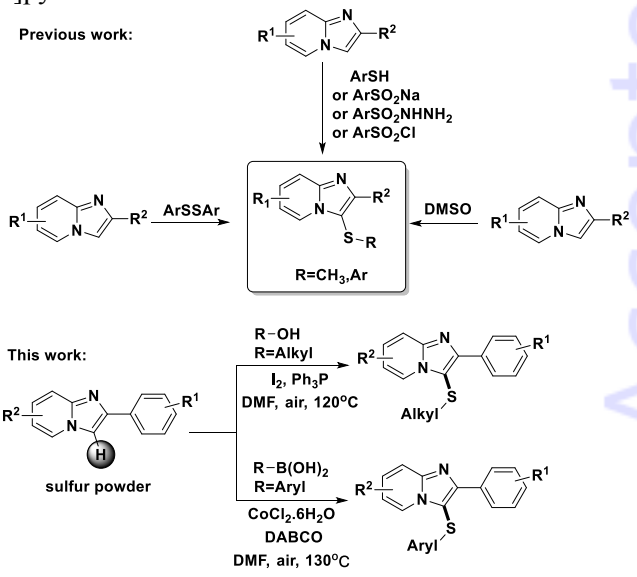
Abstract: Sulfenylation is an important transformation to generate C-S bonds in organic synthesis. Here, two three-component synthetic protocols were developed for using imidazo[1,2-α]pyridine , inorganic, odorless S_8 and alcohols or arylboronic acid as reactants to make alkyl/aryl-S-substituted imidazo[1,2-α]pyridine derivatives via C(sp^2)-H functionalization. The reactions proceeded with high efficiency and broad functional group tolerance, affording regioselective products in good yields.

Keywords: sulfenylation; imidazo[1,2-α]pyridine; C(sp^2)-H functionalization； C-S bond

Sulfenylation is an important transformation to generate C-S bonds in organic synthesis.[1] The C-S bond is also a common moiety among natural products,[2] marketed drugs,[3] pesticides,[4] and polymers.[5] Therefores, many chemists have addressed developing more efficient methods to construct C-S bonds, especially those methods which can avoid using prefunctionalized reactants, smelly and expensive sulfur agents,[6] and expensive metal catalysts. Particular attention is given to those new methods which generate C-S bond via direct C-H functionalization of reactants[7].

It's well-known that imidazo[1,2-α]pyridine is also an privileged structure in drug discovery. This core structure is associated with such biological activities, as sedative-hypnotics, gout, anticancer and Alzheimer's disease.[8] In order to find more efficient drug candidates, much effort has been devoted to generating their derivatives. Scheme 1 illustrates several methods of constructing C-S bonds on imidazo[1,2-α]pyridines that have been reported.

These methods generally involve using sulfur agents such as ArSSAr,[9] ArSH,[10] $ArSO_2NHNH_2$,[11] $ArSO_2Na$,[12] $ArSO_2Cl$.[13] All these sulfur agents are relatively expensive, and some have powerful oders. DMSO is also a sulfur agent, but only MeS-substituted derivatives can be generated.[13] Only recently, a sulfenylation method for imidazo[1,2-α]pyridines with sulfur was reported.[14] There are some shortcomings associated with these previous methods. (1) Previous methods only afford MeS- and ArS-substituted imidazo[1,2-α]pyridine derivatives. They can't make other alkyl-S-substituted derivatives by direct C-H functionalization. (2) Most of these sulfur agents are relatively expensive, odorless, and unconvenient to prepare, so they are not suitable for kilogram scale syntheses; (3) Some ArS-substituted derivatives require prefunctionalized aromatic reagents as the sulfur source. Herein, we reported two different one-pot three-component protocols for generating alkyl/aryl-S-substituted imidazo[1,2-α]pyridine derivatives via



Scheme 1. Different routes for the synthesis of 2-phenylimidazo[1,2-α]pyridine thioether derivatives.

C-H functionalization. Our methods simply use alcohols or arylboronic acids as reactants and odorless and cheap S_8 as the sulfur source. Most of

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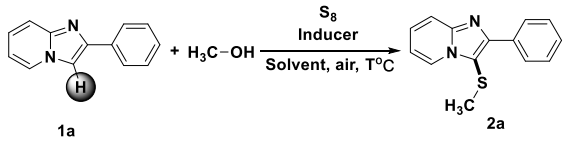
these reactions proceeded with high efficiency, affording regioselective products in good yields.

Our goal focuses on developing new sulfenylation methods using odorless and cheap sulfur agents, such as S_8, Na_2S or $Na_2S_2O_3$. The substituent connected to S at one end should also be derived from easily available chemicals to make this sulfenylation practical, environmentally friendly and efficient. Initially, alcohol and inorganic S_8 were chosen as starting materials for reaction condition screening. Different catalysts and inducers, solvents and temperatures were screened (see Table 1).

Table 1. Sulfenylation screening reactions using S_8 and methanol.[a]



Entry	Inducers/ Catalyst		T [°C]	Solvent	Yield [b] %
1	I_2	PPh_3	60	DMF	15
2	I_2	PPh_3	90	DMF	45
3	I_2	PPh_3	120	DMF	75
4	I_2	----	120	DMF	40
5	----	PPh_3	120	DMF	0
6	I_2	PPh_3	120	----	50
7	I_2	PPh_3	120	EtOAc	60
8	I_2	PPh_3	120	Toluene	40
9	I_2	PPh_3	120	Dioxane	55
10	I_2	PPh_3	120	CH_3CN	63
11	I_2	PPh_3	120	DMSO	trace
12[c]	CuI	PPh_3	120	DMF	trace
13[c]	CuI	----	120	DMF	20
14	TBAI	----	120	DMF	10
15	NH_4I	----	120	DMF	5
16	NH_4I	PPh_3	120	DMF	30
17	CCl_4	PPh_3	120	DMF	0
18	CCl_4	PPh_3	120	THF	0

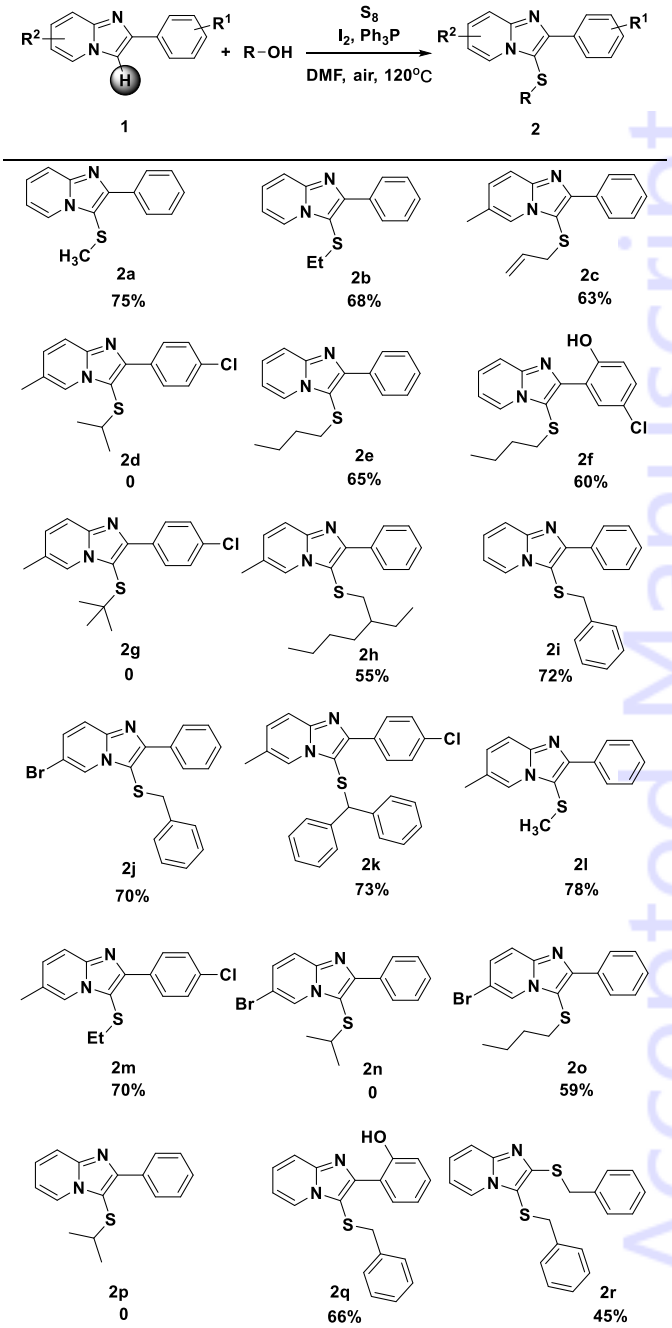
[a] *Reaction conditions:* 2-Phenylimidazo[1,2-*α*]pyridine (0.5 mmol, 1.0 equiv.), methyl alcohol (3.0 equiv.), S_8 (2.0 equiv.), inducer (1.0 equiv.), PPh_3 (1.0 equiv.), DMF (0.5 mL) under the air, 12h.

[b] Isolated yields are based on reactant **1a**.

[c] CuI (0.2 equiv.)

To start the reaction, I_2 and PPh_3 were chosen as reaction inducers in DMF at 60°C. The reaction afforded the desired product **2a** in 15% yield (entry 1, Table 1). Increasing the temperature to 90°C led to a 45% yield (entry 2). Increasing reaction temperature to 120°C gave a 75% yield (entry 3). Without using PPh_3, the reaction generated a 40% yield of expected product **2a** (entry 4). Without using I_2, the reaction didn't afford **2a** (entry 5). The combination of I_2 and PPh_3 at 120°C afforded **2a** in 50% yield under solvent-free (entry 6) conditions. If I_2 and PPh_3 were employed in ethyl acetate or toluene, the product **2a** was isolated in a 60 or 40% yield, respectively (entries 7 and 8). Using dioxane or CH_3CN as the solvent generated **2a** in a 55% or 63% yield respectively (entries 9 and 10). When DMSO was used as the solvent, trace amounts of **2a** was isolated (entry 11), despite DMSO itself being a sulfur reagent. The use of CuI (0.2 equiv.) as a catalyst with PPh_3 also failed to generate **2a** (entry 12) in DMF, but when no PPh_3 was present, a 20% yield of **2a** (entry 13) was obtained. Using tetrabutylammonium iodide (TBAI) or NH_4I as inducers, the reactions produced

Table 2. Generation of 2-phenylimidazo[1,2-α]pyridine thioether derivatives using S_8 and alcohols.[a]



[a] The reactions were carried out as follows: 2-phenylimidazo[1,2-α]pyridine (0.5 mmol, 1.0 equiv.), alcohol (3.0 equiv.), S_8 (2.0 equiv.), I_2 (1.0 equiv.), PPh_3 (1.0 equiv.), DMF (0.5 mL) at 120 °C, 12h.

[b] Isolated yields are based on reactant **1**.

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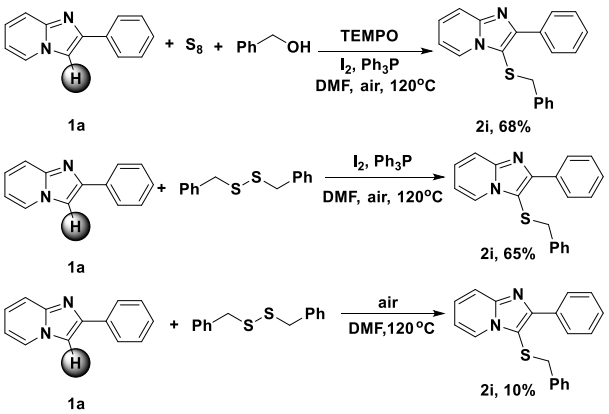
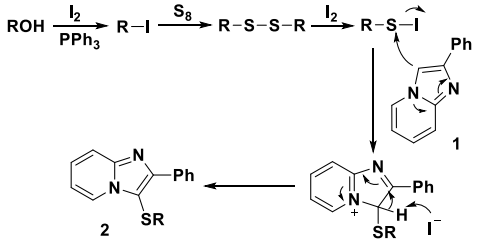
only 10% or 5% yield of **2a**, respectively (entries 14 and 15). Using the combination of NH_4I/PPh_3 in DMF gave a 30% yield of **2a** (entry 16). The combination of CCl_4 and PPh_3 in DMF at 120°C didn't give **2a** (entry 17). By changing solvent from DMF to THF, the combination of CCl_4 and PPh_3 in THF at 120°C did not afford **2a** (entry 18). After the above screening, the suitable conditions selected for the sulfenylation are: 2-phenylimidazo[1,2-a]pyridine (1.0 equiv.), alcohol (3.0 equiv.), S_8 (2.0 equiv.), I_2 (1.0 equiv.) and PPh_3 (1.0 equiv.) in DMF as the solvent at 120 °C.

Employing these selected reaction conditions, different imidazo[1,2-α]pyridines were synthesized to explore the scope of sulfenylation (Table 2). Several alcohols were also chosen as reactants. Under these conditions, all primary alcohols were suitable for sulfenylation reactions, proceeding well and generating good yields of regioselective alkyl-S-substituted imidazo[1,2-α]pyridine derivatives. But when secondary *iso*-propanol and *tert*-butanol were used as starting materials, no thioether substitution products were observed (Table 2, **2d**, **2g**, **2n**, **2p**). One exception is diphenylmethanol (secondary alcohol) which gave a 73% yield of the expected product. An elimination reaction might occur using secondary and tertiary alcohol. Allyl alcohol (Table 2, **2c**) and the phenolic OH function on benzene ring (Table 2, **2f**) were tolerated in this sulfenylation process. Neither interfered with the main sulfenylation process. Electron-donating or electron-withdrawing functions on pyridine ring also didn't cause any problems in this reaction. When unsubstituted imidazopyridine as a starting material, interestingly, the reaction gave the unexcepted disubstituted thioether product with 45% yield (Table 2, **2r**) as a main product.



Scheme 2. Control experiments.

To explore the reaction mechanism, two designed control experiments were conducted (Scheme 2). To determine if radical intermediates were involved in this sulfenylation process, TEMPO (2,2,6,6-tetramethyl-piperidinooxy) was used as a radical scavenger under the optimized conditions. In the presence of TEMPO, the reaction still gave expected **2i** in a 68% yield, indicating that the reaction was not going through a radical pathway. When **1a** was reacted with dibenzyl disulfide, the BnS-substitued product **2i** was obtained in a 65% yield. In the absence of I_2 and Ph_3P, the reaction give only a 10% yield. This indicated that dibenzyl disulfide could be a possible intermediate species involved in the reaction. Based on the above experimental results and previous reports,[15] a plausible mechanism was proposed below (Scheme 3).



Scheme 3. A plausible mechanism for the generation of alkylthioether-substituted imidazo[1,2-α]pyridine derivatives.

Alkyl iodide was probobly generated as an intermediate during the reaction between alcohol and I_2/PPh_3. This supposition is also consistent with why using primary alcohols and diphenylmethanol as reactants worked well for the sulfenylation process, but using secondary or tertiary alcohols didn't work. An elimination reaction from a secondary alkyl iodide to generate alkene would readily occur instead of reacting with S_8 to generate the disulfide. With primary alcohols, the resultant RSSR then reacted with I_2 to give electrophilic RS-I which, in turn, reacts with imidazo[1,2-α]pyridine **1** to give the RS-substituted-2-phenylimidazo[1,2-α]pyridine thioether derivatives.

To further expand the scope of this sulfenylation reaction, arylboronic acids were also tested as reactants instead of using alcohols. To find suitable conditions for this sulfenylation, different catalysts, bases, temperatures and solvents were also screened (Table 3). The initial reaction was carried out using I_2 and PPh_3 at 120°C. However, only a 5% yield of desired product was obtained after 20 h (Table 3, entry 1). When CuBr and CuI were used with Na_2CO_3, the yield increased slightly (entries 2 and 3). Using $CoCl_2 \cdot 6H_2O$ as a catalyst afforded a 40% yield of product **3a** (entry 4). Using CH_3CN or benzene as the solvent afforded only low yield of 8% or 15% (entries 5 and 6). Lowering temperature to 100°C produced a 30% yield in DMF (entry 7). Raising temperature to 130°C gave a 50% yield (entry 8). Using K_2CO_3 as a base instead of Na_2CO_3 increased the reaction yield to 63% (entry 9). The use of DBU as a base with $CoCl_2 \cdot 6H_2O$ did not generate any **3a** (entry 10) in DMF. Surprisingly, when DABCO was used as a base (entry 11), an 85% yield was obtained. Decreasing the catalyst loading to 0.2 equiv. afforded a 92% yield (entry 12), but when the catalyst loading was decreased to 0.1 equiv. , the reaction yield dropped to 80% (entry 13). When the reaction was carried out under the argon atmosphere, the yield of **3a** dropped to 60% (entry 14). Suggesting air plays a

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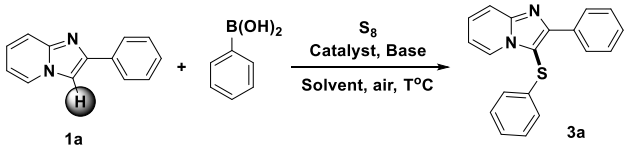
role as an oxidant, but it is not the only oxidant. Changing catalyst from $CoCl_2 \cdot 6H_2O$ to $FeCl_2 \cdot 4H_2O$ or $FeCl_3$ afforded only a 45% or 55% yield, respectively (entries 15 and 16). Based on these results, we selected the following general reaction conditions: 2-phenylimidazo[1,2-a]pyridine (1.0 equiv.), arylboronic acid (2.0 equiv.), S_8 (1.5 equiv.), $CoCl_2 \cdot 6H_2O$ (0.2 equiv.) and DABCO (2.0 equiv.) in DMF as a solvent at 130 °C.

Table 3. Sulfenylation screening reactions using S_8 and arylboronic acid.[a]

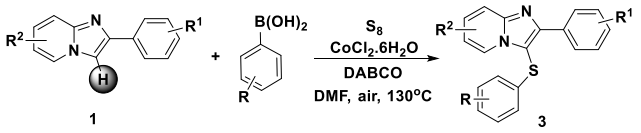


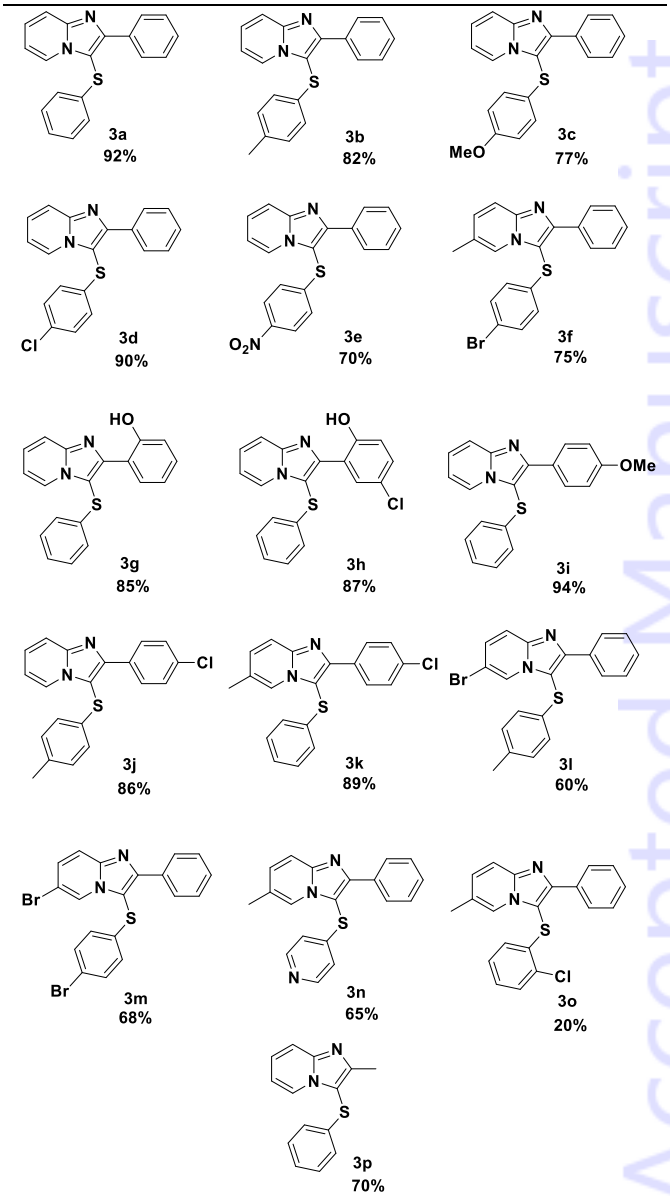
Entry	Catalyst	Base	T [°C]	Solvent	Yield [%][b]
1[c]	I_2	PPh_3	120	DMF	5
2	CuBr	Na_2CO_3	120	DMF	10
3	CuI	Na_2CO_3	120	DMF	15
4	$CoCl_2.6H_2O$	Na_2CO_3	120	DMF	40
5	$CoCl_2.6H_2O$	Na_2CO_3	120	CH_3CN	8
6	$CoCl_2.6H_2O$	Na_2CO_3	120	Benzene	15
7	$CoCl_2.6H_2O$	Na_2CO_3	100	DMF	30
8	$CoCl_2.6H_2O$	Na_2CO_3	130	DMF	50
9	$CoCl_2.6H_2O$	K_2CO_3	130	DMF	63
10	$CoCl_2.6H_2O$	DBU	130	DMF	0
11	$CoCl_2.6H_2O$	DABCO	130	DMF	85
12[d]	$CoCl_2.6H_2O$	DABCO	130	DMF	92
13[e]	$CoCl_2.6H_2O$	DABCO	130	DMF	80
14[f]	$CoCl_2.6H_2O$	DABCO	130	DMF	60
15	$FeCl_2.4H_2O$	DABCO	130	DMF	45
16	$FeCl_3$	DABCO	130	DMF	55

[a] *Reaction conditions*: 2-phenylimidazo[1,2-α]pyridine (0.5 mmol, 1.0 equiv.), arylboronic acid (2.0 equiv.), S_8 (1.5 equiv.), catalyst (0.5 equiv.), base (2.0 equiv.), DMF (0.5 mL) under the air, 20h.
[b] Isolated yields are based on reactant **1a**.
[c] I_2 (1.0 equiv.), addition: PPh_3 (1.0 equiv.).
[d] $CoCl_2.6H_2O$ (0.2 equiv.).
[e] $CoCl_2.6H_2O$ (0.1 equiv.).
[f] Under the argon atmosphere

With these selected conditions in hand, several arylimidazo[1,2-a]pyridines with different substituents were synthesized and reacted with different substituted arylboronic acids which contained (-Me, -OMe, -Cl, -Br, $-NO_2$) on their phenyl ring. These results are presented in Table 4. All these sulfenylation reactions proceeded well, giving aryl-S-substituted imidazo[1,2-α]pyridine derivatives in good yields. Furthermore, electron-donating functions on imidazo[1,2-α]pyridine ring gave somewhat higher yields than those with electron-withdrawing functions. Furthermore, the scope of arylboronic acid substrates was investigated. Using a heteroaromatic boronic acid also gave a good yield of the desired product **3n**. When ortho-chlorosubstituted arylboronic acid was used, its steric hindrance reduced the yield to 20% (Table 4, **3o**). The substituent change on imidazo[1,2-α]pyridine from an aryl to an alkyl function was also explored. When 2-methylimidazo[1,2-α]pyridine was used as a reactant, the reaction still gave a 70% yield of **3p**.

Table 4. Generation of 2-phenylimidazo[1,2-α]pyridine thioether derivatives via C-H functionalization catalyzed by $CoCl_2$ using S_8 and arylboronic acids.[a]





[a] The reactions were carried out as follows: 2-phenylimidazo[1,2-α]pyridine (0.5 mmol, 1.0 equiv.), arylboronic acid (2.0 equiv.), S_8 (1.5 equiv.), $CoCl_2.6H_2O$ (0.2 equiv.), DABCO (2.0 equiv.), DMF (0.5 mL) at 130°C, 20h.
[b] Isolated yields are based on reactant **1**.

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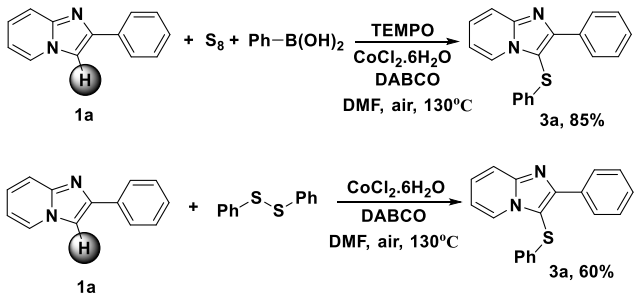
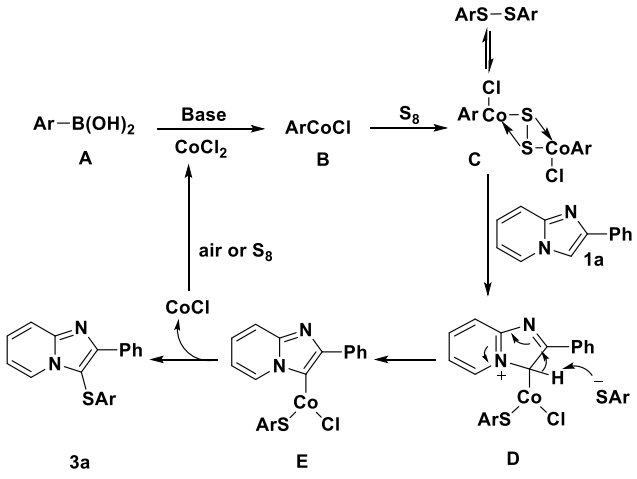
To probe possible reaction mechanisms, TEMPO was used as a radical scavenger in a control reaction (Scheme 4). A good yield was still obtained despite the presence of this radical scavenger. This is evidence that the reaction did not proceed through a radical pathway. Previous literature showed that arylboronic acids could react with S_8 to generate disulfides.[16] With this in mind, we synthesized 1,2-diphenyldisulfane, and reacted it with **1a** under the optimized conditions. As expected, a 60% yield of **3a** was isolated. This result suggested that 1,2-diphenyldisulfane could be an intermediate in the sulfenylation process.



Scheme 4. Control reactions.

On the basis of our experimental results and those of previous relevant mechanistic studies,[17] we propose the speculative but plausible reaction pathway depicted in Scheme 5. Initially, in the presence of base and $CoCl_2$, arylboronic acid **A** reacted with the cobalt dichloride catalyst to generate arylcobalt complex intermediate **B**. Subsequently, intermediate **B** reacts with S_8 powder to give another intermediate **C,** which might exist in equilibrium diaryldisulfide. **C** then reacts with **1a** to afford the intermediate **D** which is deprotonated by base (DABCO) or ArS^- to give the intermediate **E**.



Scheme 5. A plausible mechanism for the generation of arylthioether-substituted imidazo[1,2-α]pyridine derivatives.

Reductive elimination gives product **3a**. The resultant Co(I) from reductive elimination step was then oxidized back to Co(II) by air or S_8.

In summary, two one-pot three-component protocols which use easily available inorganic, odorless S_8 as a sulfur source, alcohols or arylboronic acids as reactants were developed to make alkyl/aryl-S-substituted imidazo[1,2-α]pyridine derivatives via C-H functionalization. Both reactions proceeded well, affording regioselective products in high yields under relatively mild conditions. These two protocols are practical and efficient, enriching currently known C-S bond construction methods.

Experimental Section

General experimental procedures

All reactions were carried out in round-bottom flasks; stirring was achieved with an oven-dried magnetic stirring bar. Solvents were purified by standard methods unless otherwise noted. Commercially available reagents were purchased from Aladdin Company in China and used throughout without further purification other than those detailed below. Flash column chromatography was performed on silica gel (200-300 mesh). All reactions were monitored by TLC analysis. Deuterated solvents were purchased from Cambridge Isotope laboratories. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz respectively. HRMS spectrometry (LC-HRMS) was recorded on a LXQ Spectrometer (Thermo Scientific) operating on ESI-TOF (MeOH as a solvent). Heterocyclic derivatives were synthesized according to the literature.

General procedure for the synthesis of compounds 2a-r.

2-Phenylimidazo[1,2-α]pyridine **1a** (0.5 mmol, 1.0 equiv.), S_8 (2.0 equiv.) and methyl alcohol (3.0 equiv.) were added to a dried flask with DMF (0.5 mL) , followed by the addition of I_2 (1.0 equiv.) and PPh_3 (1.0 equiv.). The mixture was stirred at 120 °C. After 12 h, the reaction was cooled to room temperature, diluted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (Petroleum ether: EtOAc = 30:1) on silica gel to give the product **2a** as a colorless oil in a 75% yield. The same procedure was applied to the production of compounds **2a-r.**

General procedure for the synthesis of compounds 3a-p.

2-Phenylimidazo[1,2-α]pyridine **1a** (0.5 mmol, 1.0 equiv.), S_8 (1.5 equiv.) and arylboronic acid (2.0 equiv.) were added to a dried flask with solvent DMF (0.5 mL) , followed by the addition of $CoCl_2.6H_2O$ (0.2 equiv.) and DABCO (2.0 equiv.). The mixture was stirred at 130 °C. After 20 h, the reaction was cooled to room temperature, diluted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified

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by flash chromatography (Petroleum ether: EtOAc =25:1) on silica gel to give the product **3a** as a colorless oil in a 92% yield. The same procedure was applied to the production of other compounds **3a-p.**

Author contributions

W.Z. and Y.D. contributed equally.

Acknowledgements

This investigation was generously supported by funds provided by Jiangsu University (1281290006). We are very grateful to Charles U. Pittman, Jr., Mississippi State University, for his assistance during the revision of the manuscript."

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10.1002/adsc.201601431

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One-pot Three-component Synthesis of Alkyl/Arylthioether-Substituted Imidazo[1,2-α]pyridine Derivatives via C(sp2)-H Functionalization

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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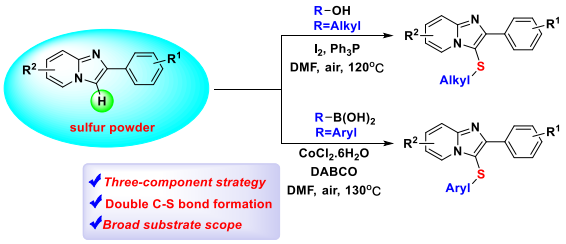

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