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Cu-catalyzed sulfenylation of imidazol[1,2-α]pyridine via C-H functionalization using a combination of $Na_2S_2O_3$ and halides

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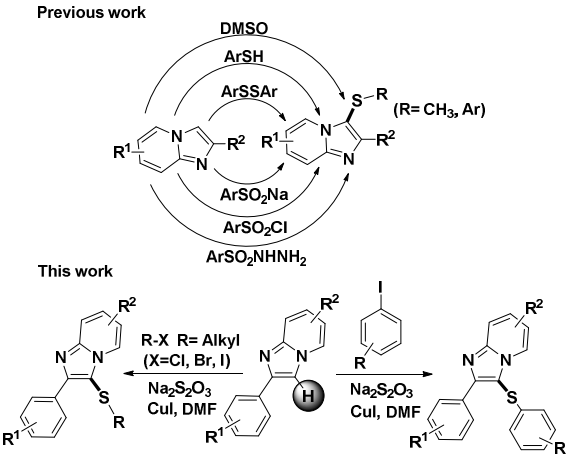
A novel copper-catalysed sulfenylation method by using inorganic salt $Na_2S_2O_3$ and alkyl halides (Cl, Br, I) or iodobenzene homologues is described. The reactions proceeded smoothly, giving regioselective 2-phenylimidazo[1,2-α]pyridine thioether derivatives in good yields via C-H functionalization process. More important, this method has extended the existing methods by offering a better method which can make both alkyl and aryl thioether derivatives under one reaction condition.

Sulfides are widely present in nature, many natural products and drugs possess sulfide function.[1] By the oxidation of sulfide functions, sulfoxides, sulfones and sulfoximines can be easily made.[2] On the other hand，imidazol[1,2-α]pyridine is also an privileged structure in drug discovery,[3] several drugs possessing this moiety have important biological activities, such as anticancer,[4] sedative-hypnotics,[5] gout[6] and Alzheimer's disease,[7] therefore, much time and effort has been addressed to the synthesis of its derivatives. Among these derivatives, thioether derivatives are very important one. Until now, several methods related to the synthesis of imidazol[1,2-α]pyridine thioether derivatives have been reported.[8] These thioether derivatives were mainly made by using these sulfur agents, such as ArSSAr,[9] ArSH,[10] $ArSO_2NHNH_2$,[11] $ArSO_2Na$,[12] $ArSO_2Cl$ and DMSO[13] with or without using transition metal catalysts. Here, we reported a new sulfenylation method of imidazol[1,2-α]pyridine by using inorganic $Na_2S_2O_3$ and different halides.

Actually, $Na_2S_2O_3$ and alkyl halide were starting materials for making Bunte salt which was first invented by Hans Bunte in 1874.[14] Traditionally, this salt was used to react with nucleophiles such as thiols, Na_2S and cyanide to generate disulfides, trisulfides and thiocyanates,[15] few people used this salt for sulfenylation reaction of other molecules via C-H functionalization process, let alone use aromatic halide and Bunte salt for sulfenylation reaction under the action of transition metal copper catalyst. In this paper, instead of using Bunte salt as reactants, $Na_2S_2O_3$[16] and halides were directly used as starting materials for sulfenylation reaction.



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

To find a suitable reaction condition for this sulfenylation, 2-phenylimidazo[1,2-α]pyridine (**1a**), *n*-butyl chloride and sodium thiosulfate ($Na_2S_2O_3$) were chosen as model substrates. Initially，when CuI was used as a catalyst in EtOAc at 120°C, only 20% yield of **2a** was obtained after 12hrs (Table 1, entry 1). No product was formed and isolated, when toluene was used as a solvent under the same reaction condition (entry 2). Using DMSO as a solvent increased the yield to 30% (entry 3). Switching solvent from DMSO to CH_3CN generated the expected product **2a** in a 45% yield (entry 4). To our delight, when DMF was employed as a solvent, the reaction gave a 75% yield in the presence of CuI catalyst (entry 5). Changing CuI into CuBr decreased the reaction yield to 59% (entry 6). But when CuCl was used as a catalyst, only 10% yield of expected product **2a** was produced (entry 7). The reaction catalysed by $CuCl_2$ didn't afford the desired product (entry 8). Using $Cu(OAc)_2$ and $CuNO_3$ gave reaction yields of 25% and

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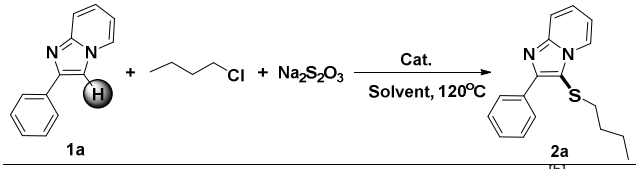
Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst (equiv.)	Solvent	Yield[b] (%)
1	CuI	EtOAc	20
2	CuI	Toluene	0
3	CuI	DMSO	30
4	CuI	CH_3CN	45
5	CuI	DMF	75
6	CuBr	DMF	59
7	CuCl	DMF	10
8	$CuCl_2$	DMF	trace
9	$Cu(OAc)_2$	DMF	25
10	$Cu(NO_3)_2$	DMF	23
11	CuO	DMF	15
12	$FeCl_3$	DMF	0

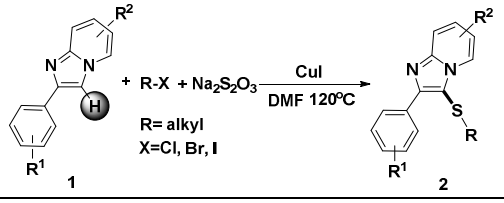
[a]*Reaction conditions:* 2-phenylimidazo[1,2-α]pyridine (1.0 mmol, 1.0 equiv.), Butyl chloride (2.0 equiv.), $Na_2S_2O_3$ (1.25 equiv.), CuI (20 mol%.), solvent (0.5 mL). [b] Isolated yields are based on 2-phenylimidazo[1,2-α]pyridine, the reaction was run for 12 hrs.

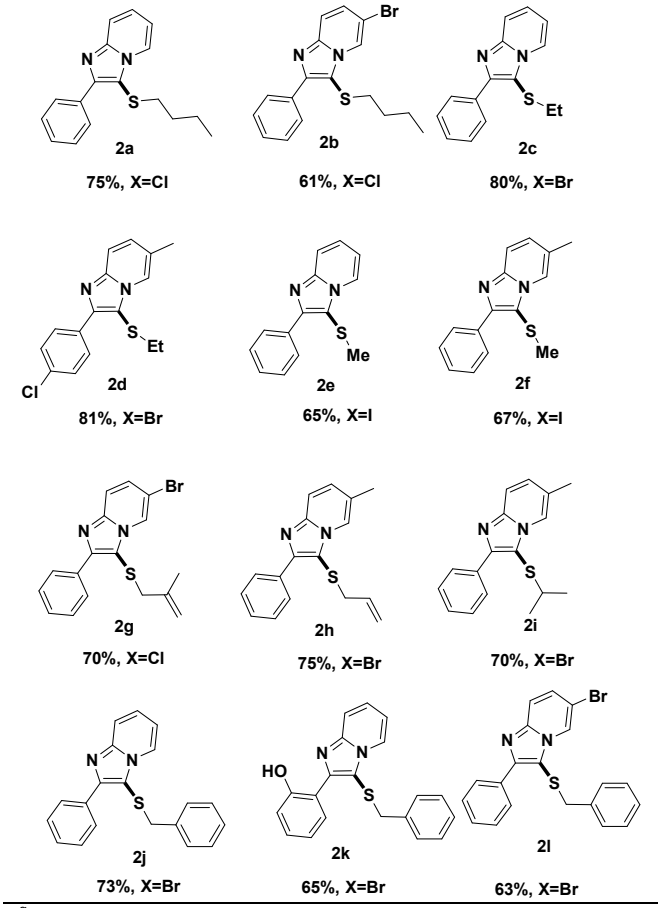
23% respectively (entries 9, 10). When CuO was used as a catalyst, only 15% yield was obtained (entry 11), the usage of $FeCl_3$ didn't give any product (entry 12). In summary, the suitable condition for the sulfenylation of 2-phenylimidazo[1,2-α]pyridine: 2-phenylimidazo[1,2-α]pyridine (1.0 equiv.), $Na_2S_2O_3$ (1.25 equiv.), butyl chloride (2 equiv.), and CuI (20 mol%), DMF was used as a solvent and the reaction temperature is 120 °C.

With a suitable reaction condition in hand, we started to determine the limitations and generality of this new sulfenylation method. In addition to 2-phenylimidazo[1,2-α]pyridine (**1a**) and *n*-butyl chloride, several other alkyl halides and 2-phenylimidazo[1,2-α]pyridine homologues were used and evaluated. It was found that all tested primary alkyl halides (Bu-Cl, CH_2=C(CH_3)CH_2Cl, EtBr, BnBr, MeI) were suitable for the sulfenylation of 2-phenylimidazo[1,2-a]pyridine (**1a**), whether they contained Cl, Br or I element in their structures, they all afforded regioselective desired products in good yields. To check if secondary alkyl halides were suitable for the sulfenylation reaction, secondary *i*-PrBr was tested as a representative halide under the same reaction condition, it was found that the reaction gave a 70% yield. To further explore if tertiary alkyl halide was feasible for this sulfenyaltion process, *t*-BuCl was also tried, but it was found that only a small amount of the expected product was produced.

To check if aryl halides could be used as reactants for this sulfenylation method, so we selected different aromatic iodobenzene as a model reactant and carried out the sulfenyaltion reaction under the same condition, it was found that this sulfenylation reaction still proceeded well, giving the desired product in a 69% yield. Without further considering for optimized reaction condition, different iodobenzene homologues including electron-donating and eletron-withdrawing substituents were used to react with different 2-phenylimidazo[1,2-α]pyridines in the presence of $Na_2S_2O_3$, all

Table 2. Generation of alkyl-S-substituted 2-phenylimidazo[1,2-α]pyridine derivatives via C-H functionalization using alkyl halides and $Na_2S_2O_3$ as reactants[a]





[a]*Reaction conditions:* 2-phenylimidazo[1,2-α]pyridine (1.0 mmol, 1.0 equiv.), alkyl chloride (2.0 equiv.), $Na_2S_2O_3$ (1.25 equiv.), CuI (20 mol%), solvent (0.5 mL). [b] Isolated yields are based on 2-phenylimidazo[1,2-α]pyridine, the reaction was run for 12 hrs.

carried-out reactions generated the expected products in good yields via C-H functionalization process, the experimental results are shown in Table 2. But when bromobenzene and chlorobenzene were also tried under the same condition, both reactions failed to provide any the corresponding thioether derivatives, This fact also explained the reason why bromide function on the structures of **2q** and **2r** didn't have any impact on the sulfenylation reactions.

In summary, we have demonstrated a copper-catalysed sulfenylation of 2-phenylimidazo[1,2-α]pyridine by using inorganic salt $Na_2S_2O_3$ and alkyl halides (Cl, Br, I) or iodobenzene homologues via C-H functionalization process. All

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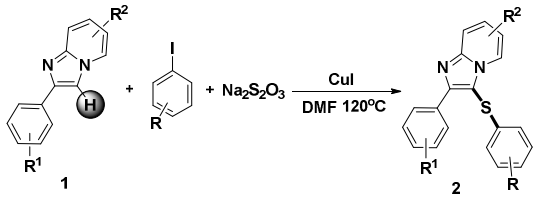
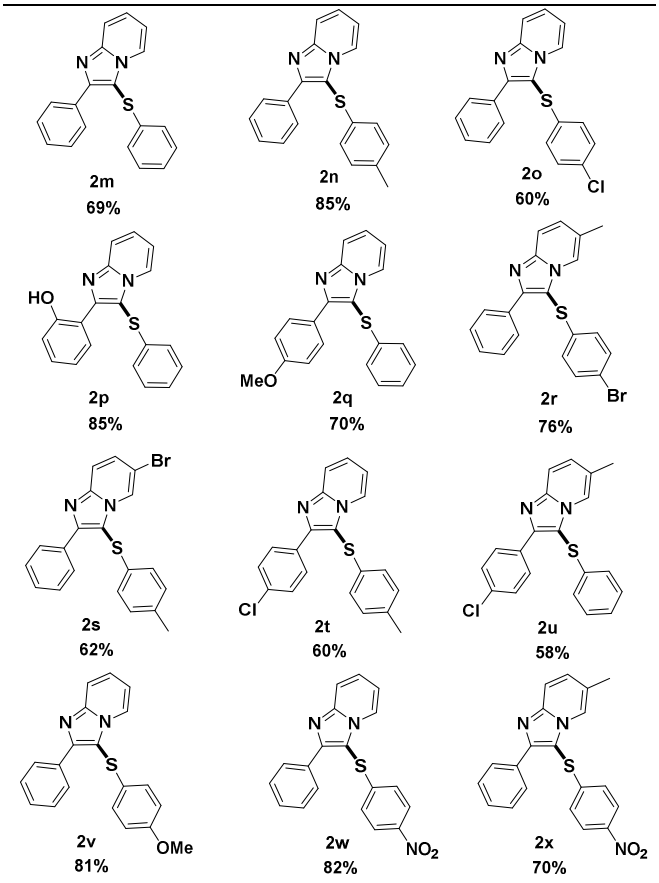
Table 3. Generation of aryl-S-substituted 2-phenylimidazo[1,2-α]pyridine derivatives via C-H functionalization using aryl halides and $Na_2S_2O_3$ as reactants[a]





[a]*Reaction conditions:* 2-phenylimidazo[1,2-α]pyridine (1.0 mmol, 1.0 equiv.), aryl chloride (2.0 equiv.), $Na_2S_2O_3$ (1.25 equiv.), CuI (20 mol%), solvent (0.5 mL). [b] Isolated yields are based on 2-phenylimidazo[1,2-α]pyridine, the reaction was run for 12 hrs.

reactions proceeded well, giving regioselective 2-phenylimidazo[1,2-α]pyridine thioether derivatives in good yields via C-H functionalization process. More important, this method has extended the existing methods by offering a general method which can make both alkyl and aryl thioether derivatives under one mild reaction condition Based on what we've found, this method might be even extended for the thioether preparation of other nucleophilic molecules, this work is currently under way in our lab.

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Graphic abstract

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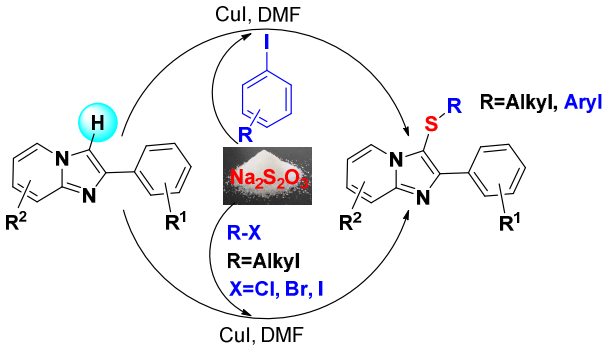

Copper-catalysed sulfenylation method by using inorganic salt $Na_2S_2O_3$