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Short communication

Copper-catalyzed thiolation of imidazo[1,2-a]pyridines with (hetero)aryl thiols using molecular oxygen

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ABSTRACT

A new and facile copper-catalyzed thiolation of imidazo[1,2-a]pyridines with (hetero)aryl thiols was developed for the formation of C–S bond by using molecular oxygen as oxidant under base-free conditions. The presented protocol has provided the selective C-3 sulfenated products with good yield. A computational study was carried out by using the B3LYP density functional theory to elucidate the regioselectivity of C-2 and C-3. Calculation results indicated that the thiolation toward C-3 was easier and smoother, which was consistent with our experiment results.

1. Introduction

Organosulfur compounds are of great significance in chemistry and biology [1,2]. Among these compounds, (hetero)aryl sulfides are useful motif, frequently found in biologically and pharmaceutically active compounds [3–5] for HIV and cancer as well as Alzheimer's and Parkinson's diseases [6,7]. Transition metal-catalyzed C–S bond forming transformation [8–13] is among the most powerful tools in organic reactions and plays a crucial role in medicinal chemistry, fine chemicals, and material science. With the development of green chemistry and increased concern over environmental issues, one of the current challenges in organic synthesis is to develop efficient, selective, and economical synthetic methods. Direct cross dehydrogenative coupling by selective functionalization of the C–H bond has developed as an efficient transformation for the formation of C–S bonds [14–19]. In recent years, the direct C–S bond formation approaches have been described by the groups of Yu [20,21], Jiang [22,23], and Deng et al. [24]. Therefore, synthesis of organosulfur compounds via catalytic direct thiolation of C–H bond has attracted and continues to attract the interest of organic chemists due to their remarkable application value in chemistry.

Imidazo[1,2-a]pyridine and its derivatives as important fine chemicals have been found to be key structural units in many natural products and drugs and has exhibited a wide range of biological activities [25–27], such as necopidem, olprinone, zolimidine, saripidem, alpidem, and zolpidem. The development of facile method for the formation of imidazo[1,2-a]pyridine derivatives is a challenging goal of organic chemists via C–H functionalization [28–31]. Very recently, Zhang [32] reported Cs_2CO_3 promoted direct C–H bond sulfenylation of imidazo[1,2-a]pyridines with diaryldisulfides in ionic liquids; Adimurthy [33] reported NCS-promoted sulfenylation of imidazo[1,2-a]pyridines with thiophenol. Herein, we developed a new and facile copper-catalyzed protocol to construct structurally sophisticated imidazo[1,2-a]pyridine derivatives via direct cross dehydrogenative coupling (Scheme 1).

2. Results and discussion

In our initial studies, 2-methylimidazo[1,2-a]pyridine (1a) and benzo[d]thiazole-2-thiol were chosen as the substrates to investigate the formation of 2-(2-methylimidazo[1,2-a] pyridin-3-ylthio) benzo[d] thiazole (3a). A variety of copper catalysts in conjunction with different oxidants, solvents, and temperatures were screened, and the results are described in Table 1. Gratifyingly, the C–H bond activation of 1a and subsequent coupling to 2a was found to proceed smoothly in DMF (3 mL) as solvent employing 5 mol% of $CuCl_2$ catalyst. The resulting cross-coupling product **3a** was obtained in 42% yield (Table 1, entry 1). Inspired by this promising result, various copper salts, such as $CuBr_2$, $Cu(OAc)_2$, CuO and $Cu(OTf)_2$ were next screened to study their catalytic efficiency for the formation of 3a (Table 1, entries 2–5). Among them, $Cu(OAc)_2$ is a more efficient catalyst than the other tested. The result encouraged us to improve the yield of the synthesis of **3a** by adding oxidant (Table 1, entries 6–10). But, the product 3a was formed with low yield or not detected in the presence of air, oxone, BQ, $K_2S_2O_8$,

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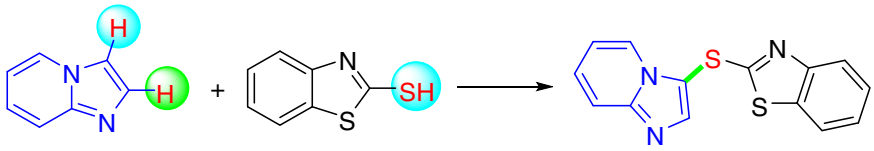
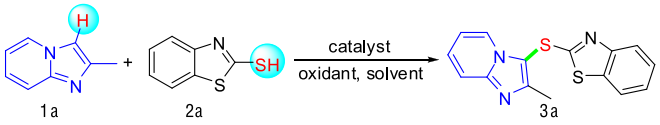


Scheme 1. Cross coupling of imidazo[1,2-a]pyridines with thiols.

Table 1
Screen of reaction conditions[a]



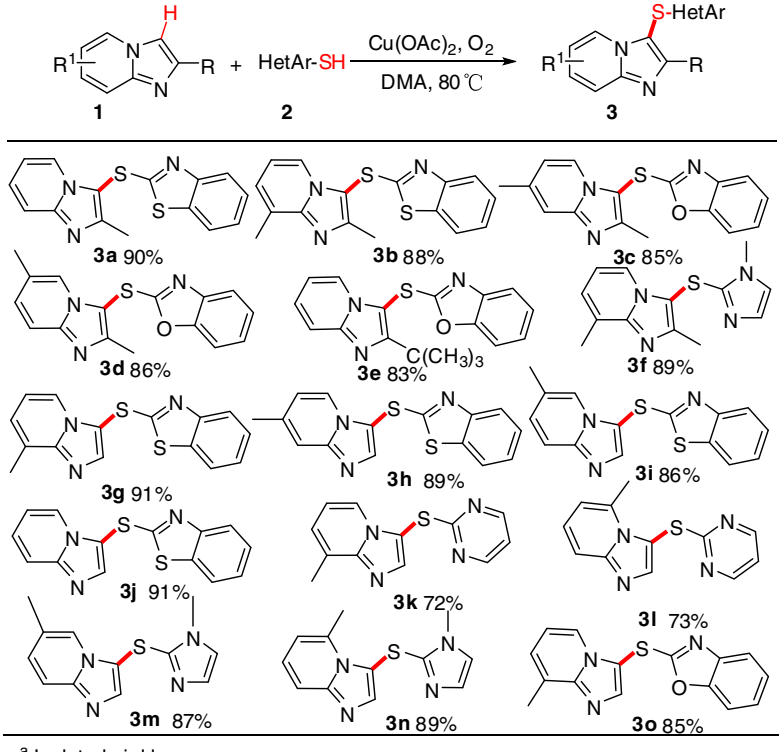
Entry	Catalyst	Oxidant	Solvent	T	Yields[b]
1	$CuCl_2$	O_2	DMF	80	42
2	$CuBr_2$	O_2	DMF	80	36
3	$Cu(OAc)_2$	O_2	DMF	80	79
4	CuO	O_2	DMF	80	21
5	$Cu(OTf)_2$	O_2	DMF	80	32
6[c]	$Cu(OAc)_2$	Air	DMF	80	78
7	$Cu(OAc)_2$	Oxone	DMF	80	15
8	$Cu(OAc)_2$	BQ	DMF	80	19
9	$Cu(OAc)_2$	$K_2S_2O_8$	DMF	80	NP
10	$Cu(OAc)_2$	AgOAc	DMF	80	50
11[c]	$Cu(OAc)_2$	O_2	DMSO	80	81
12	$Cu(OAc)_2$	O_2	NMP	80	78
13	$Cu(OAc)_2$	O_2	toluene	80	NP
14	$Cu(OAc)_2$	O_2	dioxane	80	NP
15	$Cu(OAc)_2$	O_2	DMA	80	93
16	$Cu(OAc)_2$	O_2	DMA	120	82
17	$Cu(OAc)_2$	O_2	DMA	50	64
18	$Cu(OAc)_2$	O_2	DMA	rt	NP

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.8 mmol), catalyst (5 mol%), oxidant (1.0 mmol), solvent (3.0 mL), rt-120 °C, 20 h.
[b] GCyield.
[c] O_2 or air (500 mL).

and AgOAc. The effects of solvents were next examined (Table 1, entries 11–15). Among the solvents, we were delighted to find that the corresponding product **3a** was readily formed in 93% yield in DMA. Other solvents, such as DMSO, NMP, toluene, and dioxane, were also afforded in moderate yields or not detected. Finally, the optimization of reaction temperature showed that 80 °C was optimal (entries 16–18).

With the establishment of a viable reaction system, the scope of this $Cu(OAc)_2$-catalyzed coupling reaction was further expanded. The results are described in Scheme 2. Different substituted imidazo[1,2-a]pyridine derivatives with a variety of heteroaromatic thiols were also tested. The thiols, such as benzo[*d*]thiazole-2-thiol, benzo[*d*]oxazole-2-thiol, and 1-methyl-1*H*-imidazole-2-thiol and pyrimidine-2-thiol, were tolerated, and provided the selective C-3 sulfenated products in 72–91% yields. However, the desired product was not formed, when the substrate (1*H*-benzo[*d*]imidazole-2-thiol) was used in the reaction. All the results indicated that this strategy provided a wide range of substrates to form thioether-decorated imidazo[1,2-a]pyridines in moderate to excellent yields, which can be used to prepare potential biologically important molecules.

The thiolation of 2-unsubstituted imidazo[1,2-a]pyrazines with aromatic thiols was next examined and the results are summarized in Scheme 3. All the results indicated that the selective C-3 sulfenated products were successfully formed in 81%–92% yields. The electron-rich aromatic thiols (OCH_3, CH_3) reacted smoothly to give good to excellent yields. The steric hindrance substrates, such as 2-methoxybenzenethiol, 2-chlorobenzenethiol and 2-tert-butyl-imidazo[1,2-a]pyridines, were



[a] Isolated yields

Scheme 2. Thiolation of imidazo[1,2-a]pyrazines with HetAr-SH.