



Communication

Copper-catalyzed cross-dehydrogenative coupling of pyridine N-oxides with cyclic ethers

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ABSTRACT

Highly chemo- and regioselective synthesis of 2-alkylpyridine N-oxides from pyridine N-oxides and cyclic ethers has been developed through copper-catalyzed CDC reactions using CuO as the catalyst under mild reaction conditions. Optimization study showed that, K₂S₂O₈ is the best oxidant for the reaction and the mechanistic study proved the radical pathway for this transformation. It was found that the substrates with electron donating or electron withdrawing groups could react smoothly to afford the desired products.

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1. Introduction

Transition metal-catalyzed C–H bond activation and subsequent C–C bond formations have attracted much interest in recent years [1]. Cross-dehydrogenative coupling reactions (CDC reactions) pioneered by Li, are direct oxidative C–C bond formation from two unactivated C–H bonds that eliminate the need for pre-activation of both substrates [2]. There are only a few examples for functionalization of pyridine N-oxides by CDC bond forming reactions [3]. In 2008, Chang and co-workers reported palladium-catalyzed direct arylation of pyridine N-oxides with unactivated arenes [4]. In 2009, Li and co-workers reported metal free alkylation of pyridine N-oxides with cyclohexane [5]. The reaction led to the formation of both di- and tricyclohexyl substituted products (Scheme 1, Eq. (1)). Cyclic ethers arylation process has been investigated recently. Liu reported arylation of tetrahydrofuran and 1,4-dioxane with arylboronic acids [6] and copper-catalyzed oxidative C–H/C–H coupling between simple ethers and olefins was also investigated by the same group [7]. Nickel-catalyzed alkylation and arylation of oxygen containing heterocycles was reported by Ramidi and co-workers recently [8]. Wu and Cui developed direct C-2 alkylation of quinoline N-oxides with ethers via palladium-catalyzed CDC reactions [9]. This protocol also

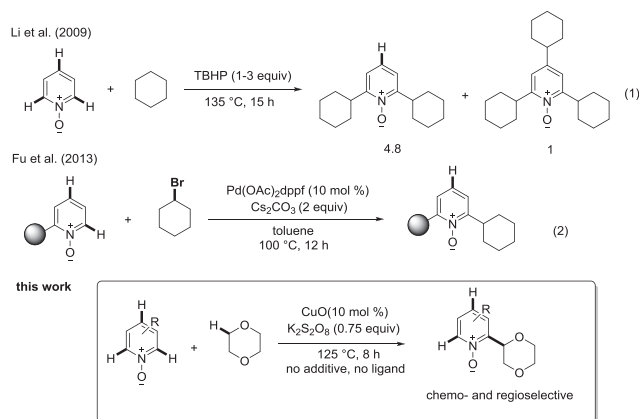
includes two examples confined to the reaction of pyridine N-oxides blocked on position 2, with ethers. More recently, Fu and co-workers reported palladium-catalyzed C–H activation/cross-coupling of quinoline N-oxides and 2- blocked pyridine N-Oxides with secondary alkyl bromides (Scheme 1, Eq. (2)) [10]. Lack of regio- and chemoselectivity is the main problem of the above mentioned methods for functionalization of pyridine N-oxide derivatives. During the completion of this work Wang and co-workers reported the oxidative cross-coupling of pyridine N-oxides and ethers under transition-metal-free conditions [11]. The reaction is performed using 4 equivalent of tert-butylhydroperoxide and 1 equivalent of potassium carbonate at 145 °C for 16 h. With the progress obtained in the field of cross dehydrogenative coupling via C–H activation reactions and as a part of our ongoing approach to extend more examples of CDC reactions [12], we were interested in exploring chemo- and regioselective synthetic routes to alkylpyridine N-oxides via CDC reactions. C–H functionalization of pyridine N-oxides using inexpensive copper catalysts has been reported rarely [13]. Herein, we report an efficient and highly regio- and chemoselective C-2 alkylation of pyridine N-oxides through copper-catalyzed cross-dehydrogenative coupling reactions.

2. Results and discussion

We began our study by evaluating various conditions for 2-alkylation of pyridine N-oxide with 1,4-dioxane (Table 1). It was

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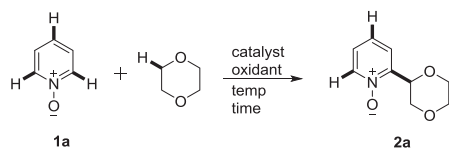
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Scheme 1. Selective approaches to alkylation of N-oxides.

found that the nature of catalyst and oxidant plays a critical role on the reaction efficiency, and no reaction took place without catalyst or oxidant (entries 20 and 21). Various metals were investigated and the best result was obtained with CuO as the catalyst. Screening showed that $K_2S_2O_8$ was the most efficient oxidant in comparison with Ag_2CO_3 (entry 19) or peroxide oxidants like TBHP and DTBP (entries 17 and 18). No desired product was observed in the absence of air (under an inert atmosphere of argon, Table 1, entry 22) which indicated an oxidative process with air was involved in the formation of the products. The yield of the reaction was not improved by increasing the reaction time beyond 8 h (Table 1, entries 3, 8, 9). Finally, the reaction proceeded highly efficiently when 10 mol % of CuO was used in combination with 0.75 mmol of $K_2S_2O_8$ (entry 3).

Table 1
Optimization of the reaction conditions^a.



Entry	Catalyst	Oxidant	Time (h)	T (°C)	Yield (%)
1	CuBr ₂	K ₂ S ₂ O ₈	8	125	65
2	Cu(OAc) ₂ ·H ₂ O	K ₂ S ₂ O ₈	8	125	51
3	CuO	K ₂ S ₂ O ₈	8	125	87
4	CuI	K ₂ S ₂ O ₈	8	125	12
5	Cu ₂ O	K ₂ S ₂ O ₈	8	125	23
6	CuCO ₃	K ₂ S ₂ O ₈	8	125	35
7	CuSO ₄	K ₂ S ₂ O ₈	8	125	17
8	CuO	K ₂ S ₂ O ₈	16	125	81
9	CuO	K ₂ S ₂ O ₈	4	125	38
10	CuO	K ₂ S ₂ O ₈	8	60	0
11	CuO	K ₂ S ₂ O ₈	8	140	56
12	CuO	K ₂ S ₂ O ₈	8	100	26
13	[Ru(p-cymene)Cl ₂] ₂	K ₂ S ₂ O ₈	8	125	trace
14	FeCl ₃	K ₂ S ₂ O ₈	8	125	0
15	NiBr ₂	K ₂ S ₂ O ₈	8	125	0
16	CuO	(NH ₄) ₂ S ₂ O ₈	8	125	81
17	CuO	TBHP	8	125	15
18	CuO	DTBP	8	125	0
19	CuO	Ag ₂ CO ₃	8	125	0
20	—	K ₂ S ₂ O ₈	8	125	0
21	CuO	—	8	125	0
22 ^b	CuO	K ₂ S ₂ O ₈	8	125	0

^a All the reactions were carried out in the presence of 1 mmol of 1a, catalyst (10 mol %) and oxidant (0.75 equiv) in 1,4-dioxane (2 cc).

^b Under argon atmosphere.

Increasing the amounts of catalyst and oxidant did not affect the reaction efficiency. This reaction is highly site-selective and no regioisomeric product of **2a** was observed under the reaction conditions. The chemoselectivity of the reaction is interestingly high and the reaction doesn't suffer from double or triple alkylation.

With the optimized conditions in hand, we next investigated the substrate scope of this protocol (Table 2).

It was found that the substrates with electron donating (such as $-CH_3$ and $-Et$) or electron withdrawing groups (such as COMe and COOEt) could react smoothly to afford the desired products. Unfortunately, the reaction with linear ethers was not successful. To confirm the radical pathway for the synthesis of the desired products radical-trapping experiments were conducted. When **1a** was treated with TEMPO (2,2,6,6-tetramethylpiperidine-N-oxyl), as a radical-inhibitor, formation of the desired product **2a** was totally suppressed. On the basis of the above-mentioned results and literature reports, a plausible mechanism for the copper-catalyzed 2-alkylation of pyridine N-oxides is illustrated in Scheme 2 [14]. As shown metallization of pyridine N-oxide derivative with Cu(II) generates intermediate A. Radical intermediate B is generated in situ by hydrogen atom abstraction of the cyclic ether carried out by sulfate radical anion produced from the heated potassium peroxodisulfate. The reaction of intermediate A with intermediate B gives Cu(III) complex C which reductively eliminates to the desired product **2a** and Cu(I). Cu(I) undergoes air oxidation to yield higher oxidation state Cu(II).

3. Conclusion

In summary, an efficient and convenient synthetic route with high regio- and chemoselectivity for the synthesis of 2-alkyl pyridine N-oxides, which are important structural motifs in pharmaceutical and agrochemical products, from pyridine N-oxides and cyclic ethers via copper-catalyzed reactions has been developed. Optimization study showed that, $K_2S_2O_8$ is the best oxidants for the reactions and mechanistic study proved the radical pathway for the transformations.

4. Experimental

4.1. General information

Copper catalysts, $K_2S_2O_8$, pyridine and ether derivatives were purchased from Merck. Unless otherwise indicated, all reagents were purchased from commercial distributors and used without further purification. Thin layer chromatography (TLC) analysis was performed using Silicycle precoated TLC plates (silica gel 60 F254). The products were purified by preparative column chromatography on silica gel (0.063–0.200 mm; Merck). IR Spectra: Shimadzu FT-IR-4300 spectrometer; in cm^{-1} . ¹H and ¹³CNMR Spectra: were recorded on Bruker DRX-600, 500, 400 and 300-Advance instrument in CDCl₃; δ in ppm, J in Hz. High resolution mass spectra were obtained with a Kratos Concept I IH mass spectrometer.

4.2. A general procedure for the synthesis of 2-alkyl pyridine N-oxides

An oven-dried test tube equipped with a magnetic stir bar was charged with pyridine N-oxides (1 mmol), CuO (8 mg, 10 mol %), $K_2S_2O_8$ (200 mg, 0.75 mmol), cyclic ethers (2 cc) and then it was sealed with a silicone septa screw-cap. The reaction was allowed to proceed for 8 h at 125 °C. The reaction mixture was then diluted with DCM and filtered. Organic layer was dried over Na₂SO₄, concentrated under vacuum, and purified by column

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