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Acid-Free Silver-Catalyzed Cross-Dehydrogenative Carbamoylation of Pyridines with Formamides

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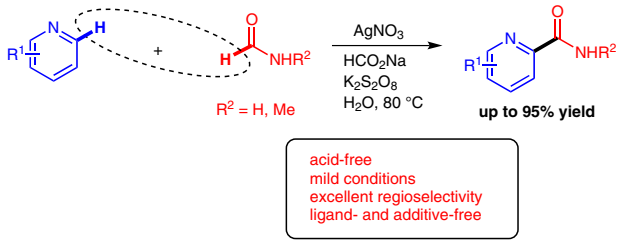

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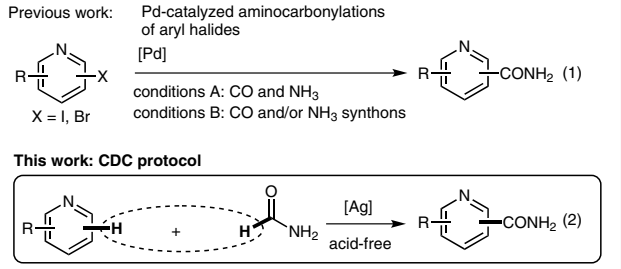
Abstract Primary pyridylcarboxamides are prevalent parent structures in bioactive molecules and have the apparent advantages over N-protected derivatives as synthetic building blocks. However, no practical methods have been developed for direct synthesis of this compound class from unfunctionalized pyridines. We herein present a general, safe, concise, acid-free, and highly selective method for the C2-carbamoylation of pyridines with unprotected formamide and *N*-methyl formamide through the cleavage of two C–H bonds.

Key words pyridylcarboxamides, pyridines, C–H bonds functionalization, carbamoylation, formamides

Primary pyridylcarboxamides are widely used as versatile building blocks for pharmaceuticals and herbicides owing to the innate advantages of these free N–H groups over N-protected derivatives in synthetic manipulations and their unique biological activity.[1] As a result, numerous methodologies have been developed for primary pyridylcarboxamides. Generally, these compounds are constructed by reacting carboxylic acids or benzoic acid derivatives (e.g., acyl chlorides, anhydrides, and esters) with ammonia, albeit producing stoichiometric amounts of waste.[2] To overcome these disadvantages, the atom-economic palladium-catalyzed aminocarbonylation of aromatic halides with ammonia has utilized as an alternative and attractive strategy (Scheme 1, eq. 1: conditions A).[3] However, the required handling of two toxic, flammable, and/or corrosive gases [carbon monoxide (CO) and ammonia] and high-pressure equipments restrict their large-scale applications. Although aqueous ammonia[4] and some sophisticated ammonia equivalents[5] have been demonstrated to prepare aromatic primary amides, such as hexamethyldisilazane (HMDS), *N*-*tert*-butylamine, benzylamine, allyl amine, hydroxylamine, and a titanium–nitrogen complex; these methods are inaccessible to direct synthesis of primary pyridylcarboxamides. Up to date, there are limited examples for the direct synthesis of primary pyridylcarboxamides via palladium-catalyzed aminocarbonylations of aryl halides with ammonia equivalents. Recently, Bhanage et al. reported methoxylamine hydrochloride undergoing sequential carbonylation and demethoxylation in the presence of $PdCl_2$ (10 mol%) and CO (5 atm) to construct amide groups.[6] Furthermore, the Skrydstrup group employed ammonium carbamate as ammonia synthon and 9-methyl-9*H*-fluorene-9-carbonyl chloride (COgen) as CO source to synthesize primary pyridylcarboxamides by a two-chamber system.[7] Recently, Baburajan and co-workers used nongaseous precursors NH_4Cl and $Co_2(CO)_8$ for both ammonia and CO, respectively.[8] These protocols are attractive as both the NH_3 and CO sources can readily be handled. However, these more sophisticated synthons cause higher cost and lower atom efficiency (Scheme 1, eq. 1: conditions B). Noteworthy progress is that formamide acts both as the NH_3 and CO surrogate for carbamoylation of aryl halides, although a high temperature (120–180 °C) and a strong base are required to ensure the decomposition of the formamide into CO and ammonia.[9] In all above-mentioned methods, the use of preactivated starting materials (often aryl iodides/bromides), thus adding multistep procedures towards the construction of one desired chemical bond, make this protocol unfavorable in both the environment and large-scale applications (Scheme 1, eq. 1).

The ideal way to address those issues is to direct functionalization of pyridyl C–H bonds via cross-dehydrogenative coupling (CDC) approach.[10] However, unlike various reliable means for the C–H carbamoylation of other (hetero)arenes,[11] the methods for introducing amido groups into pyridine rings through pyridyl C–H decoration suffer from the following inherent difficulties:[12] (1) the low reactivity of pyridine rings because of their poor electron density,



Scheme 1 Strategies for the construction of primary pyridylcarboxamides

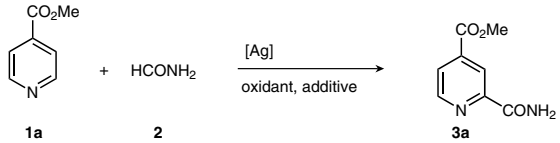
particularly, at the C-2 and C-6 positions; (2) the strong tendency of pyridines to bind to transition-metal centers leading to metal catalysts sequestration and deactivation; and (3) the regiocontrol of pyridine C–H functionalization. A seminal work reported by Li and co-workers described the palladium-catalyzed twofold C–H cross-dehydrogenative coupling of preactivated isoquinoline *N*-oxides or quinoline *N*-oxides with formylamides.[13] Unfortunately, this approach has been totally unsuccessful with pyridyl C–H bonds.

Among the known NH_3 and CO equivalents, formamide is an ideal carbamoylation reagent only if its C–H bond can be functionalized effectively, since it is inexpensive, stable, easily to handle, and almost no waste formation after cross-dehydrogenative coupling. While a number of reports are available on direct activation of N-protected formamide C–H bond,[14] catalytic C–H functionalization of formamide has met with no success to date, probably because of uncompatibility of free N–H groups.[15] Although few examples reported direct carbamoylation of pyridines with formamide, these contributions suffer from some limitations, such as low yields (often less than 50%), low chemoselectivity, narrow scope of pyridine substrates, and/or the use of severely corrosive acids.[16]

Recently, we reported a novel combination of palladium-silver-copper-mediated dehydrogenative cross-couplings of benzazoles with azoles,[17] and uncovered silver played a critical role in regiocontrol of C–H bonds activation in both substrates. Herein, we reveal the first silver-catalyzed dual C–H oxidation–cross-coupling of pyridines with formamide to a library of primary pyridylcarboxamides (Scheme 1, eq. 2). Notably, this method offers an operationally simple, inherently safe, highly efficient, and regioselective conversion process without the requirement of preactivated substrates, designed ligands, and a huge excess of pyridines.

Initially, we started our investigation by examining silver-catalyzed carbamoylation of methyl isonicotinate (**1a**) with formamide (**2**, Table 1). Gratifyingly, a carbamoylated product **3a** was obtained in 52% yield with perfect C2 regioselectivity (no appreciable amount of isomers in our crude product was found) in the presence of Na_2CO_3. And each

Table 1 $AgNO_3$-Catalyzed Carbamoylation of **1a** with Formamide[a]



1a **2** **3a**

Entry	[Ag]	Oxidant	Base	Yield of **3a** (%)
1	$AgNO_3$	$K_2S_2O_8$	Na_2CO_3	52
2	–	$K_2S_2O_8$	Na_2CO_3	0
3	$AgNO_3$	–	Na_2CO_3	0
4	$AgNO_3$	$K_2S_2O_8$	–	0
5	AgOAc	$K_2S_2O_8$	Na_2CO_3	43
6	$AgBF_4$	$K_2S_2O_8$	Na_2CO_3	39
7	AgOTf	$K_2S_2O_8$	Na_2CO_3	41
8	$AgNO_3$	$K_2S_2O_8$	Cs_2CO_3	55
9	$AgNO_3$	$K_2S_2O_8$	$NaHCO_3$	67
10	$AgNO_3$	$K_2S_2O_8$	HCOONa	95 (79)[b]
11	$AgNO_3$	TBHP	HCOONa	0
12	$AgNO_3$	BPO	HCOONa	5
13	$AgNO_3$	DTBP	HCOONa	41
14[c]	$AgNO_3$	$K_2S_2O_8$	HCOONa	89
15[d]	$AgNO_3$	$K_2S_2O_8$	HCOONa	95
16	$AgNO_3$	$K_2S_2O_8$	AcONa	91
17	$AgNO_3$	$K_2S_2O_8$	*t*-BuONa	<5
18	$AgNO_3$	$K_2S_2O_8$	Et_3N	78
19	$AgNO_3$	$K_2S_2O_8$	*i*-Pr_2NEt	80
20	$AgNO_3$	$K_2S_2O_8$	DBU	83

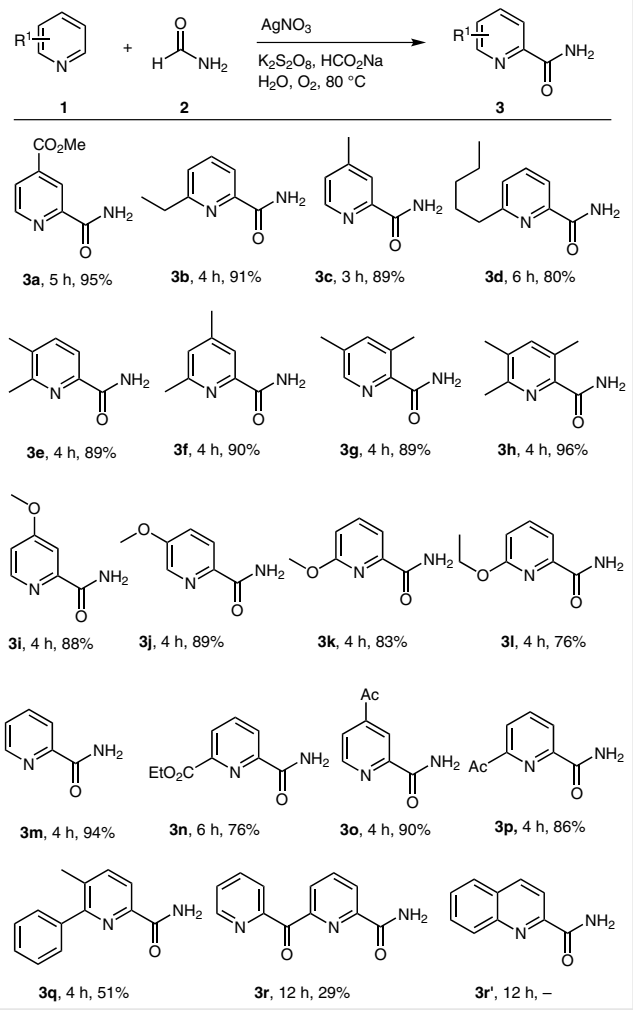
[a] Reaction conditions (unless otherwise stated): **1a** (0.5 mmol), **2** (2 mL), [Ag] (20 mol%), oxidant (1.5 mmol), base (1.0 mmol), O_2 (1 atm), 120 °C, 4 h.
[b] Conditions: $AgNO_3$ (10 mol%).
[c] Conditions: 8 h in air.
[d] Conditions: 5 h at 80 °C.

component in the combination was necessary to the reaction. We also examined other silver catalysts, such as AgOAc, $AgBF_4$, and AgOTf (Table 1, entries 5–7), and found that these catalysts provided a little bit lower yields than $AgNO_3$. Other bases such as Cs_2CO_3 and $NaHCO_3$ resulted in moderate yields of **3aa** (Table 1, entries 8 and 9). To our delight, a weak base HCOONa was found to be the most effective, affording the product **3a** in 95% isolated yield (Table 1, entry 10). Additionally, AcONa, Et_3N, *i*-Pr_2NEt, and DBU were also good bases for this transformation (Table 1, entries 16 and 18–20). However, a strong base *t*-BuONa was completely ineffective in the reaction (Table 1, entry 17). TBHP, BPO (dibenzoyl peroxide), and DTBP (di-*tert*-butyl peroxide) as the oxidants did not enable the reaction to perform well (Table 1, entries 11–13). In the air atmosphere, the reaction also proceeded effectively, providing

the desired product in 89% yield in eight hours (Table 1, entry 14). Gratifyingly, decreasing the reaction temperature to 80 °C had little impact on the transformation (Table 1, entry 15).

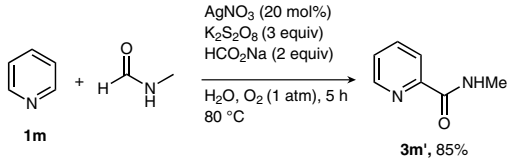
Under the optimized conditions, we next set out to explore the scope of the $AgNO_3$-catalyzed carbamoylation of pyridines with formamide. We initially investigated the carbamoylation of 2-ethylpyridine (**1b**), However, to our disappointment, a 70/28 (C2/C4) mixture of isomers was observed (see the Supporting Information). According to previous reports,[18] solvent played an important role in influencing the regioselectivity of pyridines. Water is an ideal solvent and was chosen to regulate regioselectivity. Much to our delight, an excellent C2 regioselectivity (Table S1, entry 3) could be achieved when the volume ratio of water to formamide was increased to 2:10, whereas when the amount of water was further raised, the C2 regioselectivity would decrease accordingly (Table S1, entries 4 and 5).

Subsequently, under the newly established optimal conditions, we conducted carbamoylative reactions on a variety of commercially available pyridines (Scheme 2).[19] Generally, both electron-donating and electron-withdrawing groups at the *ortho*, *meta*, or *para* position of pyridines were compatible, affording the corresponding carbamoylated products in satisfactory yields with high levels of C2 selectivity (minor C4-products: <10%). High substituent compatibility was also observed: for instance, Me, Et, MeO, EtO, COMe, COOMe, COOEt, aryl, and *n*-pentyl groups, on the pyridine moiety were tolerated well. 2-Ethylpyridine and 2-pentylpyridine provided C2-selective pyridylcarboxamides in 91% and 80% yields (**3b** and **3d**), respectively. It was found that a pyridine with a methyl at C4 position gave the desired product in a higher yield of 89% (**3c**). Pyridines having two methyl substituents at different positions on the pyridine ring could undergo the expected C2 carbamoylation in excellent yields (**3e**–**g**), and the positions of two methyl substituents had negligible impact on these reactions. A pyridine substrate with three methyl groups was quite reactive toward formamide **3h**. Furthermore, alkoxy-substituted pyridines were also surveyed: pyridine with a methoxy at C4, C3, or C2 position gave a higher yield than that with an ethoxy at C2 position (**3i**–**l**); it was worth noting that 3-methoxypyridine just provided 5-methoxypicolinamide in 89% yield (**3j**), suggesting that less steric hindrance position was far more reactive. Gratifying, a simple pyridine with multiple reactive sites with no steric hindrance still proceeded in excellent C2 selectivity (**3m**). Notably, electron-withdrawing ester and ketone groups on the pyridine ring that usually reduces reactivity and selectivity significantly[20] were tolerated and resulted in high yields with high selectivity in our case (**3a** and **3n**–**p**), and these groups are versatile handles for further transformations. While employing 3-methyl-2-phenylpyridine as a coupling partner, surprisingly, only the C2-selective carbamoylated product was obtained (**3q**) and nitrogen atom-directed product was not observed. For other substrates, di(pyridin-2-yl)methanone afforded a low yield (**3r**) and quinoline was unsuitable for this system to result in a complex mixture. To highlight the applicability of this method, the model reaction was scaled up to 5 mmol under normal conditions, which furnished the desired product **3a** in 88% yield.

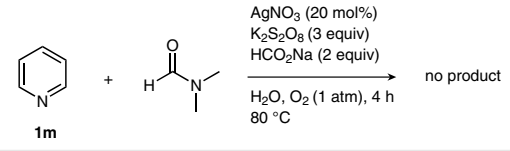


Scheme 2 Ag-catalyzed carbamoylation of pyridines with formamide. *Reagents and conditions* (unless otherwise stated): **1** (0.5 mmol), **2** (2 mL), $AgNO_3$ (20 mol%), HCOONa (1.0 mmol), $K_2S_2O_8$ (1.5 mmol), H_2O (0.4 mL), O_2 (balloon), and 80 °C. Yields are of isolated product after column chromatography.

Next, the carbamoylation of other formamides was investigated. Applying the optimized conditions to *N*-methylformamide resulted in pyridylcarboxamide **3m′** in 85% yield within five hours (Equation 1). However, when the formamide substrate was switched to DMF, its reaction with pyridine (**1m**) did not occur (Equation 2).

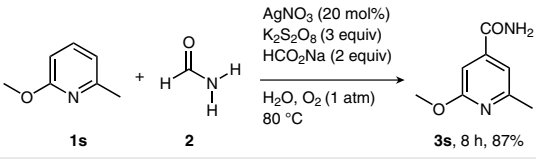


Equation 1

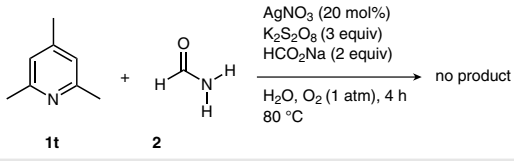


Equation 2

Considering that the above substrates proceeded in excellent C2 selectivity, we also briefly surveyed other pyridines where C2 positions were blocked by substituents. When 2-methoxy-6-methylpyridine (**1s**) was subjected to the normal conditions, only the C4-selective carbamoylated product **3s** was detected (Equation 3), demonstrating the strong preference for pyridines without C2 positions to react at the C4 position in this transformation. Furthermore, 2,4,6-trimethylpyridine, lacking of C2 and C4 positions, did not furnish desired product (Equation 4); instead it delivered an unidentifiable side product. In conjunction with all the above results, a conclusion can be made that in the carbamoylation C2 and C4 positions of pyridines are ready to react and reactivity of C2 position has much greater preference than that of C4 position, as is observed in the Chichibabin reaction.[21]



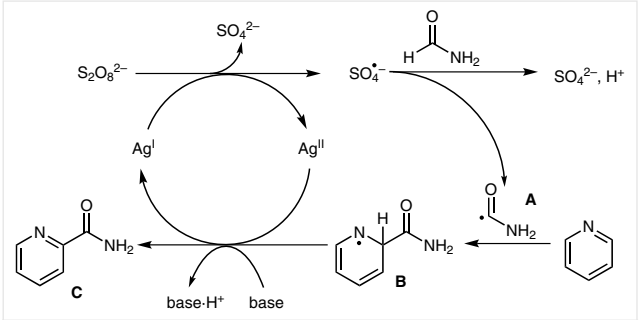
Equation 3



Equation 4

To gain preliminary insight into the mechanism of the transformation, we carried out a kinetic isotope effect (KIE) study (see the Supporting Information). The KIE value (k_H/k_D = 1.0) for C2 position of **1m** indicated that the rate-limiting step does not involve the C–H cleavage of the pyridine. Furthermore, the reaction of **1a** was totally inhibited in the presence of the radical scavenger TEMPO (see the Supporting Information). This evidence supports that the present transformation proceeds by a radical process, which is consistent with the mechanism of metal-catalyzed oxidation reactions involving persulfates.

Based on the above observations and previous research,[21–23] the following mechanism is proposed (Scheme 3). It is known[23] that the silver(I) salt can be oxidized to a silver(II) species by peroxydisulfate, and meanwhile, the peroxydisulfate disproportionates into a sulfate dianion and a sulfate radical anion. Subsequently, the sulfate radical anion oxidizes formamide to form acyl radical **A**. It is probable that the acyl radical **A** reacts with pyridine to give important intermediate **B**. Finally, the intermediate **B** is reoxidized by silver(II) and provides the carbamoylative product **C** and meanwhile, regeneration of the silver(I) species completes the catalytic cycle.



Scheme 3 Possible mechanism of oxidative carbamoylation of pyridine with formamide

In summary, we presented the first example of a ligandless silver-catalyzed direct oxidative C–H/C–H carbamoylation of pyridines with unprotected formamide for the preparation of primary pyridylcarboxamides. Advantages of our procedure include the concise and safety of operation, and in fact it is a carbon monoxide and ammonia-free route, avoiding the use of toxic and flammable, or corrosive reagents. Moreover, an excellent selectivity was achieved in the presence of water. Although excess formamide is required, it can be readily recycled for the next reactions. Primary pyridylcarboxamides are prevalent parent structures in druglike and/or pharmaceutically relevant molecules and have the clear advantages over N-protected derivatives as synthetic building blocks.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561975.

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(19) **General Procedure**

A 25 mL Schlenk flask was charged with $AgNO_3$ (17.2 mg, 20 mol% Ag), $K_2S_2O_8$ (408 mg, 1.5 mmol), and HCOONa (129 mg, 1.0 mmol) before standard cycles of evacuation and back-filling with dry and pure oxygen (three times). Corresponding pyridine **1m** (40 μL, 0.5 mmol), formamide (**2**, 2 mL), and H_2O (0.4 mL) were added successively. The mixture was stirred at 80 °C for the indicated time (monitored by TLC). At the end of the reaction, the reaction mixture was cooled to room temperature, poured into a sat. aq NaCl solution (15 mL), and extracted with EtOAc (3 × 15 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The residue was purified by flash column chromatography on silica gel (eluent: PE–EtOAc–Et_3N) to afford the corresponding product **3m** as white solid (57 mg, 94%); mp 102–103 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.62 (m, 1 H), 8.11 (br s, 1 H),

8.06 (dt, *J* = 7.6, 0.8 Hz, 1 H), 8.0 (td, *J* = 7.6, 1.6 Hz, 1 H), 7.64 (br s, 1 H), 7.61–7.57 (m, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.5, 150.7, 148.9, 138.1, 126.9, 122.4 ppm.

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