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ARTICLE TYPE

Copper-catalyzed highly efficient oxidative amidation of aldehydes with 2-aminopyridines in aqueous micellar system

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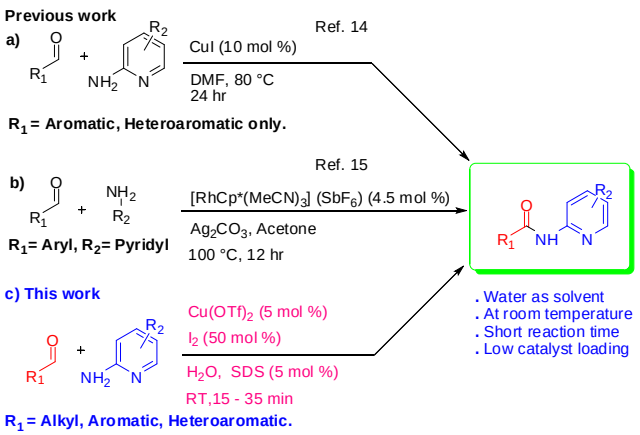
An environmentally benign protocol for the synthesis of *N*-(pyridine-2-yl)amides from aldehydes and 2-aminopyridines has been developed under mild reaction conditions. This approach requires $Cu(OTf)_2$ as a catalyst, inexpensive molecular iodine as an oxidant under anionic micellar catalysis in aqueous medium at room temperature.

The amide linkage is a key chemical connection in synthetic organic chemistry, natural polymers (peptides and proteins) and pharmaceuticals.[1] Amides are widely applicable intermediates for the synthesis of a diverse range of medicinally important molecules.[2] Conventionally, amides are accessed by treating amines with activated carboxylic acids and are limited to harsh reaction conditions, use of hazardous reagents, and generation of excess amount of by-products.[3] Recently, several innovative strategies, including the Staudinger reaction[4] and hydrative coupling reaction of alkynes with azides,[5] have emerged. Additionally, several direct oxidative amidation methods have been reported in recent past from the reaction of aldehydes,[6,7] alcohols,[8] alkynes,[1c,9] esters,[10] and anhydrides[11] with amines to furnish amides. Among all, oxidative amidation of aldehydes with amines are of great interest in synthetic organic chemistry because of atom economy and easy availability of substrates. However, these reactions usually need harsh reaction conditions, inert atmosphere, and anhydrous organic solvents. Thus, an eco-friendly protocol for amide synthesis in aqueous media would be highly desirable.

In view of green chemistry, water is the most abundant, cost effective, and environmentally benign solvent, used in organic synthesis.[12] Aqueous reactions demonstrate unique selectivity and reactivity when compared to organic solvents.[12c] However, these reactions have limitations due to poor solubility and sensitivity of organic reagents in water. Micellar system can improve the solubility of reagents, thereby accelerating the reaction rate due to the aggregation of reactants in unique micellar environment.[12b,13]

Recently, Huang *et al.*[14] reported the synthesis of *N*-(pyridine-2-yl)amides using CuI (10 mol %) in DMF at 80 ºC for 24 h (Scheme 1a). Luo *et al.*[15] also reported the Rh(III) catalyzed synthesis of *N*-pyridinamides in acetone at 100 ºC for 12 h (Scheme 1b). However, these methodologies suffer from several drawbacks, such as harsh reaction conditions, long reaction time, and use of hazardous solvents. In addition, these approaches were limited only to aryl aldehydes.



Scheme 1. Different methods to synthesize *N*-(pyridine-2-yl)amides.

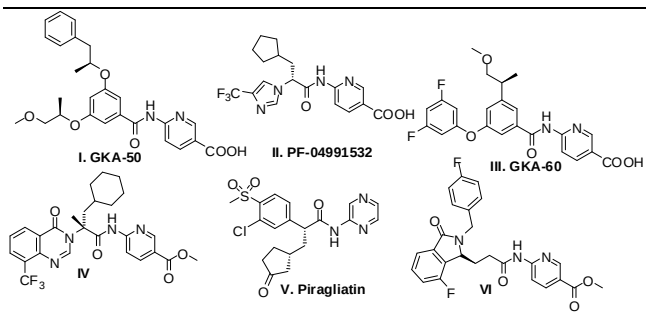


Figure 1. Selected antidiabetic agents that have progressed into clinical trials.

In continuation of our research on the development of eco-friendly protocols,[16] herein, we report a copper-catalyzed mild

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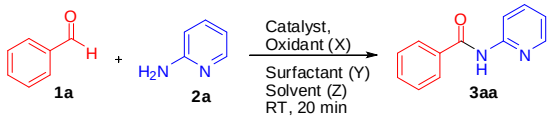
and rapid dehydrogenative cross-coupling approach for the synthesis of *N*-(pyridine-2-yl)amides *via* coupling of aldehydes with 2-aminopyridines using sodium dodecyl sulfate (SDS) in water. SDS is an important amphiphilic surfactant, which forms micelles in aqueous media[13a] and catalyzes various organic reactions.[12c,13b,17]

It is important to note that *N*-(pyridine-2-yl)amides can act as small molecule glucokinase activators (Figure 1).[18] GKAs activate the glucokinase enzyme to convert glucose into glucose-6-phosphate selectively in the liver and pancreas to confirm its potential role in the treatment of type-2-diabetes.[18a] Many pharmaceutical companies are currently working to develop potential and safe glucokinase activators.[18a,19]

Table 1. Optimization of reaction conditions.[a,i]

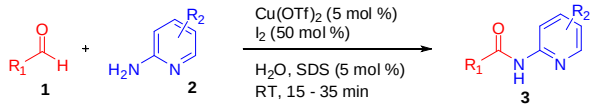


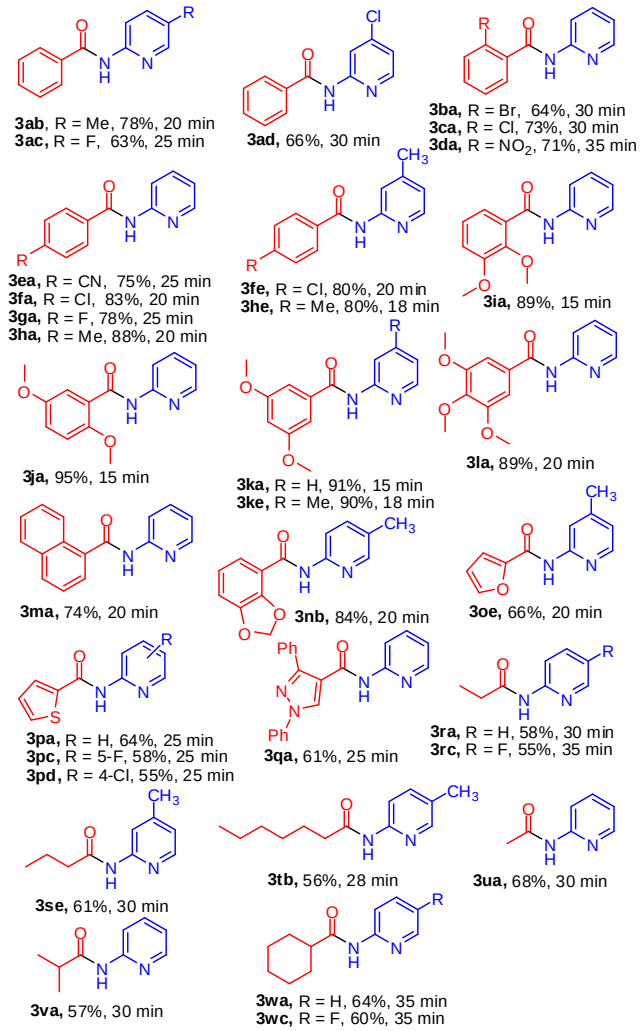
Entry	Catalyst (10 mol %)	X (1 equiv)	Y (30 mol %)	Z	Yield[b] (%)
1	$Cu(OTf)_2$	I_2	-	H_2O	30
2	$Cu(OTf)_2$	I_2	SDS	H_2O	85
3	$FeCl_3$	I_2	SDS	H_2O	10
4	$CuBr_2$	I_2	SDS	H_2O	80
5	CuI	I_2	SDS	H_2O	50
6	CuBr	I_2	SDS	H_2O	57
7	$Cu(OTf)_2$	$K_2S_2O_8$	SDS	H_2O	18
8	$Cu(OTf)_2$	TBHP	SDS	H_2O	10
9	$Cu(OTf)_2$	PIFA	SDS	H_2O	NR
10	$Cu(OTf)_2$	DDQ	SDS	H_2O	NR
11	$Cu(OTf)_2$	O_2	SDS	H_2O	NR
12	$Cu(OTf)_2$	I_2 (0.5 eq)	SDS	H_2O	93
13	$Cu(OTf)_2$	I_2(0.2 eq)	SDS	H_2O	60
14	$Cu(OTf)_2$	I_2 (0.5 eq)	PF 127	H_2O	40
15	$Cu(OTf)_2$	I_2 (0.5 eq)	Tween 80	H_2O	55
16	$Cu(OTf)_2$	I_2 (0.5 eq)	TBAB	H_2O	10
17	$Cu(OTf)_2$	I_2 (0.5 eq)	TBAI	H_2O	NR
18	$Cu(OTf)_2$	I_2 (0.5 eq)	SLS	H_2O	88
19	$Cu(OTf)_2$[c]	I_2 (0.5 eq)	SDS[f]	H_2O	92
20	**$Cu(OTf)_2$[c]**	**I_2 (0.5 eq)**	**SDS[g]**	**H_2O**	**93**
21	$Cu(OTf)_2$[c]	I_2 (0.5 eq)	SDS[h]	H_2O	70
22	$Cu(OTf)_2$[d]	I_2(0.5 eq)	SDS[g]	H_2O	75
23	$Cu(OTf)_2$[e]	I_2(0.5 eq)	SDS[g]	H_2O	40
24	$Cu(OTf)_2$[c]	I_2 (0.5 eq)	-	DCM	27
25	$Cu(OTf)_2$[c]	I_2 (0.5 eq)	-	DMF	20
26	$Cu(OTf)_2$[c]	I_2 (0.5 eq)	-	CH_3CN	62
27	$Cu(OTf)_2$[c]	I_2 (0.5 eq)	-	Toluene	30

[a] Reaction conditions: **1a** (0.93 mmol), **2a** (1.39 mmol), catalyst (10 mol %), X (1 equiv.) and Y (30 mol %) at RT, 20 min., under air. [b] Isolated yields based on **1a**. [c] 5 mol %, [d] 3 mol %, [e] 1 mol % $Cu(OTf)_2$. [f] Y 10 mol %, [g] 5 mol %, [h] 1 mol %. NR = No Reaction. [i] Abbreviations used in table: SDS = Sodium dodecyl sulfate; PF 127 = Pluronic F 127; Tween 80 = Polyoxyethylene(20)sorbitanmonooleate (Polysorbate 80); TBAB = Tetra-*n*-butyl ammonium bromide; TBAI = Tetra-*n*-butyl ammonium iodide; SLS = Sodium lauryl sulfate.

Initially, we commenced our studies with commercially available benzaldehyde (**1a**) and 2-aminopyridine (**2a**) as the model substrates to optimize the reaction conditions. In the presence of $Cu(OTf)_2$ (10 mol %) and I_2 (1.0 equiv.) in water at room temperature furnished desired product **3aa** in 30% yield (Table 1, entry 1). To our delight, when we used SDS (30 mol %) in the reaction, an enhancement in product yield was observed (Table 1, entry 2). In light of these results, a series of metal salts, namely $Cu(OTf)_2$, $FeCl_3$, $CuBr_2$, CuI and CuBr, were investigated (entries 2-6). Among all, $Cu(OTf)_2$ displayed the highest catalytic activity (entry 2).

Table 2. Synthesis of *N*-(pyridine-2-yl)amides under the optimum reaction conditions.[a, b]





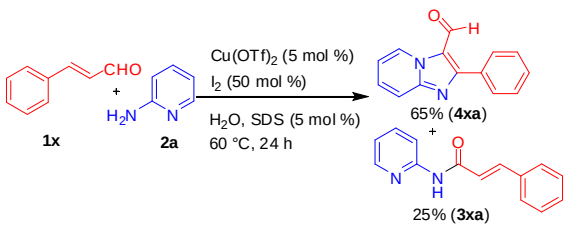
[a] Reaction conditions: **1** (0.93 mmol), **2** (1.39 mmol), $Cu(OTf)_2$ (5 mol %), I_2 (50 mol %) and SDS (5 mol %) in 4.0 mL of water at room temperature. [b] Isolated yields based on **1**.

Next, a variety of oxidants, namely $K_2S_2O_8$, TBHP, PIFA, DDQ, and O_2, were screened in the reaction. However, none of them were found to be more efficient than I_2 (Table 1, entries 7-11 vs. 2). Further optimization of I_2 loading revealed that 50 mol % of iodine produced the best yield of the desired product (entries 2,

12-13). Next, the effect of surfactants on the reaction was examined and only anionic surfactant (SDS) was found to be most suitable for this transformation whereas neutral and cationic surfactants failed to improve the yield of product (entries 14-17 vs. entry 12). This might be due to the stabilization of copper catalyst with anionic dodecyl sulfate by the formation of a $Cu(DS)_2$ complex.[20] Interestingly, optimization of surfactant loading revealed that 5 mol % of SDS is enough to this reaction (entries 19-21).

Subsequently, the effect of solvents was examined and the water was found to be a superior solvent over other organic solvents (Table 1, entries 20 vs. 24-27). To our surprise, decreasing the catalyst loading to 5 mol % led to the formation of the amide product in 93% yield (entry 20). Further decreasing the amount of catalyst to 3 mol % and 1 mol % afforded declined yields 75% and 40%, respectively (entries 22-23).

With the optimal conditions (Table 1, entry 20) in hand, we next probe the scope and generality of this oxidative amidation approach to a variety of aldehydes and 2-aminopyridines. Initially, a set of aldehydes, including aromatic and aliphatic aldehydes, were employed in the reaction and the results are summarized in Table 2. The reaction was compatible with a variety of substituents (CH_3, OCH_3, F, Cl, Br, CN and NO_2) on the aryl aldehyde moiety and furnished the products in moderate to excellent yields (**3ba-3la**). It is worth noting that halogens, CN and NO_2 groups are very important substituents for post-diversification in medicinal chemistry. The aldehydes bearing electron-donating groups provided better yields than electron-withdrawing groups (**3ia-3la** vs. **3ba-3ga & 3fe**). Sterically hindered substituent such as Br at the *ortho*-position of benzaldehyde gave the lower yield of product **3ba**. Following the aryl aldehydes, various heterocyclic aldehydes were well tolerated and furnished the corresponding products in moderate to good yields under optimal reaction conditions (**3oe-3qa**). Subsequently, a variety of aliphatic aldehydes such as acetaldehyde, propionaldehyde, butyraldehyde, heptaldehyde, isobutyraldehyde and cyclohexanal were also tested in this reaction and delivered the corresponding products in good yields (**3ra-3wc**). The lower yields in case of aliphatic aldehydes when compared to aromatic aldehydes, may be due to the side reactions such as aldol condensation and oxidation to the corresponding carboxylic acids.

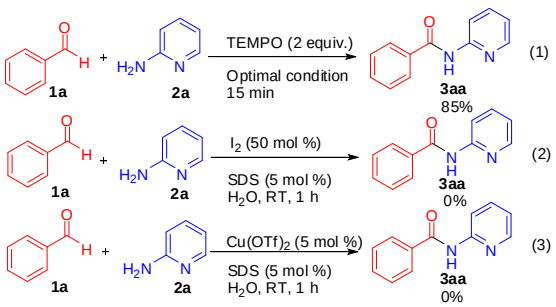


Scheme 2. Synthesis of 2-phenylimidazo[1,2-a]pyridine-3-carbaldehyde.

Next, we investigated the substrate scope of various 2-aminopyridines under the standard reaction conditions. The 2-aminopyridines containing a variety of substituents (H, CH_3, Cl and F) were well tolerated to this transformation and led to the formation of desired products in high yields. The results are summarized in Table 2. Unfortunately, no desired products were observed when different anilines (4-chloroaniline and 4-methylaniline), 3-aminopyridine, 4-aminopyridine, piperidine, 2-aminobenzimidazole, 2-aminopyrimidine, cyclohexylamine, and *n*-butylamine were used under optimized reaction conditions.

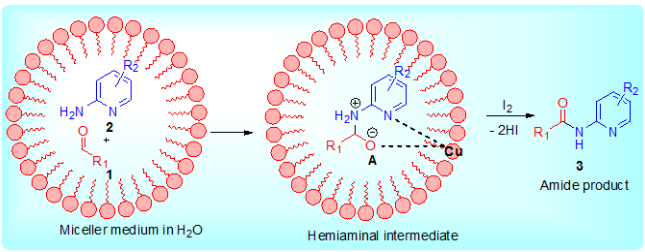
To demonstrate the generality of the present approach, we performed the reaction of *trans*-cinnamaldehyde (**1x**) with 2-aminopyridine (**2a**) under identical reaction conditions and only trace amount of amide product (**3xa**) was formed. Interestingly, when we carried out the reaction at 60 ºC for 24 h, 2-phenylimidazo[1,2-a]pyridine-3-carbaldehyde (**4xa**) was isolated as a major product and *N*-(pyridine-2-yl)cinnamamide as a minor product (Scheme 2).

Imidazo[1,2-a]pyridine and its derivatives exhibit a broad range of biological activities and are considered to be key structural scaffolds in variety of natural products and drugs such as zolpidem, alpidem, necopidem, zolimidine, saripidem and olprinone.[21] Notably, formyl group of **4xa** is an important precursor to synthesize anxiolytic drug necopidem.[22]



Scheme 3. Control experiments.

Furthermore, in order to investigate the reaction mechanism, some control experiments were performed (Scheme 3). The reaction of benzaldehyde with 2-aminopyridine, in the presence of a radical inhibitor such as TEMPO (2,2,6,6-tetramethylpiperidine 1-oxy) had no significant effect on the yield of the desired product (Scheme 3, eq 1), indicating the absence of a radical mechanism. When the reaction was performed without $Cu(OTf)_2$, the reaction failed to deliver the desired product (Scheme 3, eq 2). The amide product was also not formed in the absence of I_2 (Scheme 3, eq 3). These results collectively indicated the importance of metal catalyst and oxidant in this reaction.



Scheme 4. Proposed reaction mechanism.

According to the control experiments described above and previous literature reports,[6g,14,23] a proposed mechanistic pathway

is depicted in Scheme 4. Initially, the reaction commences with the nucleophilic addition of 2-aminopyridine (**2)** to aldehyde (**1**), leading to the formation of hemiaminal intermediate (**A**), which upon oxidation in presence of I_2, delivers the desired amide product (**3**).

In summary, we devised an eco-friendly and mild protocol for the synthesis of *N*-(pyridine-2-yl)amides from aldehydes with 2-aminopyridines by using $Cu(OTf)_2$ as a catalyst and I_2 as an oxidant under micellar system in water. The present work offers several practical advantages such as the use of mild reaction conditions, short reaction time, absence of base and ligand, under air, and easy workup procedure. In addition to previously reported methods,[14,15] we demonstrated that aliphatic aldehydes were well tolerated under optimal reaction conditions. Further synthesis of a library of new diversified *N*-(pyridine-2-yl)amides are under progress to evaluate their biological potential.

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Copper-catalyzed highly efficient oxidative amidation of aldehydes with 2-aminopyridines in aqueous micellar system

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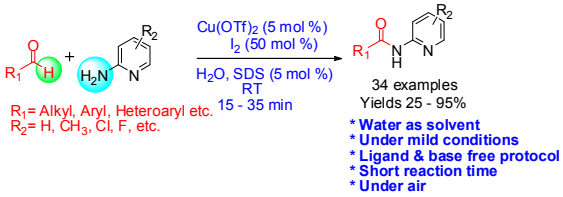

An environmentally benign protocol for the synthesis of *N*-(pyridine-2-yl)amides from aldehydes and 2-aminopyridines has been developed under mild conditions.