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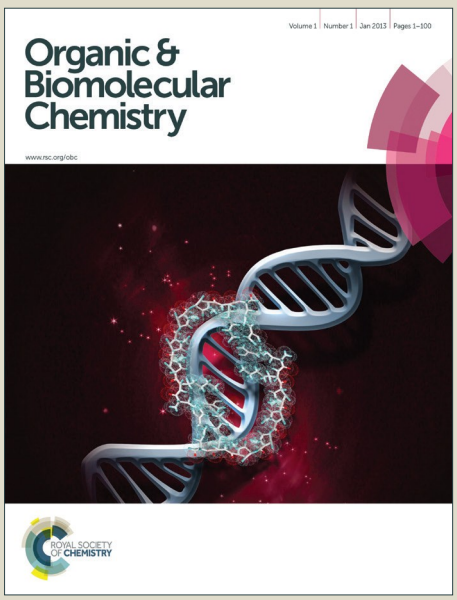

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Metal-free oxidative amidation of aldehydes with aminopyridines employing aqueous hydrogen peroxide

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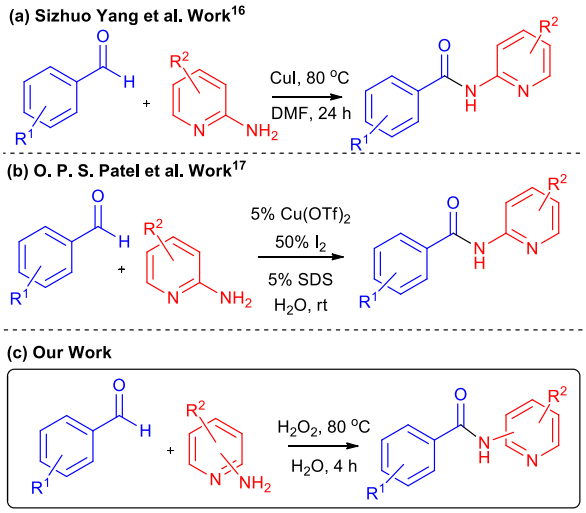
First metal free report on the amidation of aldehydes with aminopyridines was accomplished using simple aqueous hydrogen peroxide (aq. H_2O_2) as the oxidant. No catalysts or additives were needed for this transformation and the reaction proceeded in water, an environmentally benign reaction medium. Green oxidant and reaction conditions, and the ability to construct diverse *N*-(pyridin-2-yl)benzamide by this elegant method render it to be a practical alternative for the synthesis of these amides.

Formation of amide bond is an important task in organic synthesis as amide functionality is widespread in various natural products and pharmaceuticals that exhibits several biological activities.[1] Conventional methods for the generation of amide bond involve the reaction of activated carboxylic acid or its derivatives with amines.[2] Due to several drawbacks associated with these methods, including generation of stoichiometric amount of by products, various alternative strategies have been devised. Carboxylic acid is usually obtained as the result of oxidation of aldehydes or alcohols and application of aldehydes as starting material appears to be economically viable route for the synthesis of amide. Thus oxidative amidation of aldehydes with amines in presence of transition metal catalysts and stoichiometric amount of oxidant proves to be a convenient synthetic strategy.[3-6] Apart from the metal catalysed oxidative amidation, organocatalytic amidation was also performed employing N-heterocyclic carbene (NHC) catalysis.[7] In addition, catalyst-free oxidative amidation were also reported using *tert*-butyl hydroperoxide (TBHP)[8] or oxone[9] as oxidants. In spite of being advantageous over conventional methods, these protocols have innate drawbacks like harsh reaction conditions, stoichiometric use of base and expensive oxidant hence there is scope for devising efficient strategies. We have recently reported NHC-catalysed oxidative amidation of aldehydes with amines [7c] and are on the process of developing cleaner and greener oxidative amidation protocol with inexpensive oxidants. Aqueous hydrogen peroxide (aq. H_2O_2) proves to be the oxidant of interest as it is economically cheap and greener and it produces water as the by-product. Till date, there are only two reports on the oxidative amidation of aldehydes employing aq. H_2O_2 reported where aldehyde is coupled with cyclic secondary amines to generate amides under normal conditions[10] and under continuous flow micro-reactor systems.[11]



Scheme 1 . Synthesis of *N*-(Pyridin-2-yl)benzamide from aldehyde and 2-aminopyridine.

N-(Pyridin-2-yl)benzamide moiety is an important pharmacophore found widely in many bioactive compounds, identified as a luciferase inhibitor,[12] found to be effective for the treatment of osteoporosis,[13] and as anti-ulcer agent.[14] 4-*N*-pyridin-2-yl-benzamides based fluorescent *para*-aminobenzoic acid (PABA) nanotubes was found to possess dual property, as a delivery vehicle of therapeutic agents and acting as a therapeutic agent by itself.[15] *N*-(Pyridin-2-yl)benzamide was

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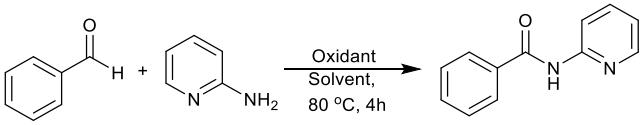
previously synthesized via CuI catalysed dehydrogenative reaction between aldehyde and aminopyridine (Scheme 1a).[16] An alternate method employs $Cu(OTf)_2$ as a catalyst in presence of I_2 as an oxidant under anionic micellar catalysis in aqueous medium for the synthesis of aforementioned amides (Scheme 1b).[17] A heterogeneous approach for the synthesis *N*-(Pyridin-2-yl)benzamide was achieved by employing Cu_2O and CuI supported on multi-walled carbon nanotubes (MWCNTs).[18] However, to the best of our knowledge, metal-free oxidative amidation for the synthesis of *N*-(pyridin-2-yl)benzamide has never been explored. Herein, we present the first metal free oxidative amidation of aryl aldehydes with aminopyridines-a primary amine, in presence of aq. H_2O_2 as the terminal oxidant using water as the green and environmentally benign reaction medium (Scheme 1c).

Results and discussion

In order to arrive at the optimized reaction condition for the synthesis of *N*-(pyridin-2-yl)benzamides, benzaldehyde and 2-aminopyridine were taken as the model substrates (Table 1). Initially, when TBHP in water was taken as the oxidant for this coupling in water at 80 °C, the yield was only 38% (entry 1). Then variation of different oxidants were performed and it was observed that oxidants like Di-*t*-Butyl Peroxide (DTBP), *tert*-Butyl peroxybenzoate (TBPB) and Dicumyl Peroxide (DCP) fared poorly under the present reaction condition (entries 2-4). When aq. H_2O_2 was taken as the oxidant, surprisingly the yield of the desired product was increased to 91% (entry 5). In the absence of oxidant, the desired amide was not observed (entry 6). Once we fixed the suitable oxidant for this reaction, we diverted our attention to find out the suitable solvent for this oxidative amidation. Polar solvents like H_2O, DMF and CH_3CN gave comparatively good yields (entries 5, 7 and 8). In case of non-polar solvents, other than toluene, the yields are marginal (entries 9-13). Finally, we arrived at water as the reaction medium for this amidation strategy due to its environmentally benign nature and other advantages (entry 5). When the reaction was performed at room temperature, the yield of the desired product was decreased drastically (entry 14). Gradual increase in the temperature increases the product yield and the yield was optimal at 80 °C and further rise in the temperature above 80 °C doesn't increase the product yield (entries 5, 15-17). When the reaction was performed with 2 equiv. of oxidant, the yield of the desired product decreased suggesting that 3 equiv. of oxidant is needed to carry out the reaction (entry 18).

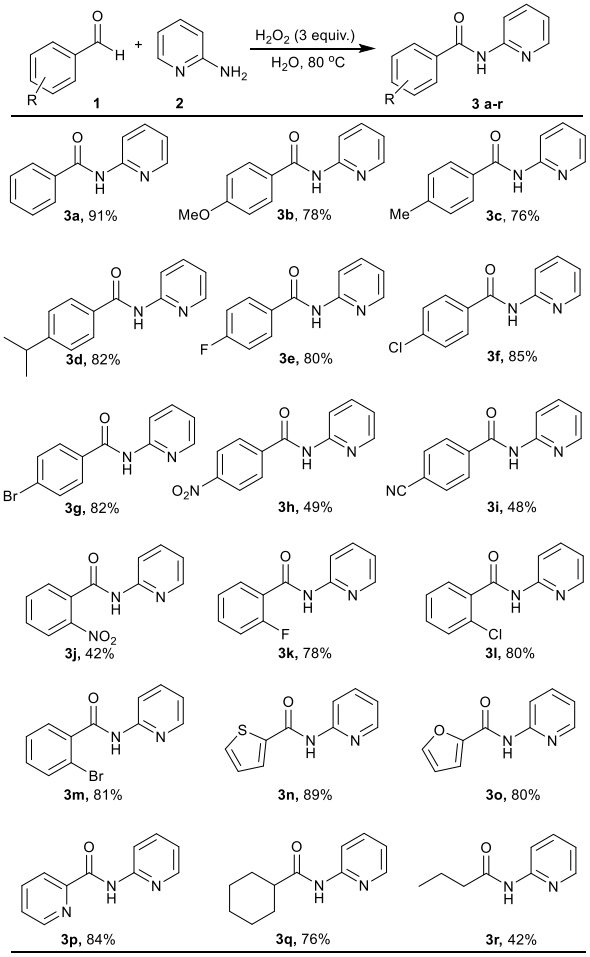
Table 1. Optimization of reaction conditions for H2O2 mediated oxidative amidation. a



Entry	Oxidant	Solvent	Yield (%)[b]
1	TBHP	H_2O	38
2	DTBP	H_2O	32
3	TBPB	H_2O	<5
4	DCP	H_2O	NR
5	**H_2O_2**	**H_2O**	**91**
6	--	H_2O	NR
7	H_2O_2	DMF	64
8	H_2O_2	CH_3CN	87
9	H_2O_2	Toluene	83
10	H_2O_2	PhCl	37
11	H_2O_2	Dioxane	21
12	H_2O_2	EtOH	23
13	H_2O_2	THF	13
14	H_2O_2[c]	H_2O	48
15	H_2O_2[d]	H_2O	56
16	H_2O_2[e]	H_2O	79
17	H_2O_2[f]	H_2O	81
18	H_2O_2[g]	H_2O	66
19	H_2O_2[h]	H_2O	77
20	H_2O_2[i]	H_2O	74

[a]Reaction Conditions: Aldehyde (1.0 mmol), aminopyridine (1 mmol), oxidant (3 equiv.), solvent (2 mL), 80 °C, 4 h. [b]I solated yield. [c] Reaction at rt. [d] Reaction at 40 °C. [e] Reaction at 60 °C. [f] Reaction at 100 °C. [g] Reaction with 2 equiv. of oxidant. [h] Reaction time 3 h. [i] Reaction time 5 h.

Table 2. Scope of aldehydes for the oxidative amidation with 2-aminopyridine.[a]

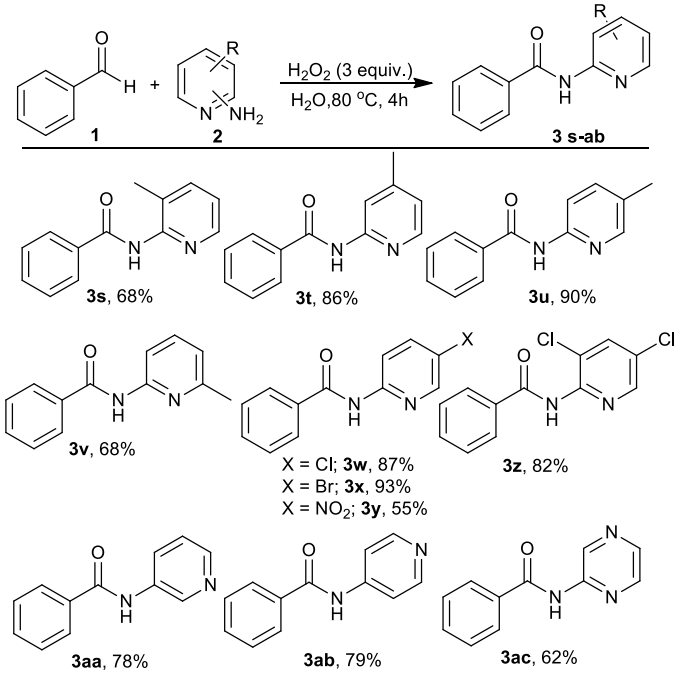


[a]Reaction Conditions: Aldehyde (1.0 mmol), 2-aminopyridine (1.0 mmol), oxidant (3 equiv.), solvent (2 mL), 80 °C, 4 h, Isolated yield.

The product yield decreased when the reaction was carried out for 3 h and if it is prolonged for 5 h, the yield decreased marginally due to the formation of acid under the reaction condition (entries 19 and 20). Thus we arrived at the optimized reaction condition: aq. H_2O_2 (3 equiv.) in H_2O at 80 °C for 4 h.

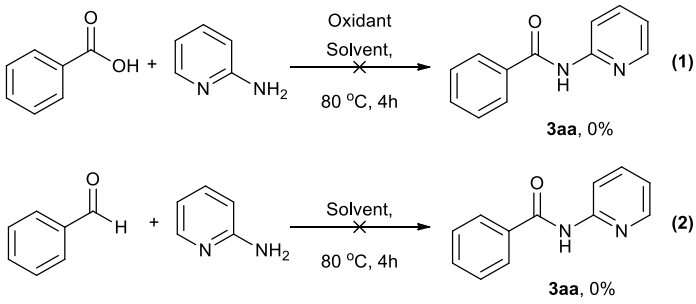
To explore the scope of this metal-free process, various aldehydes were coupled with 2-aminopyridine under the optimized reaction condition (table 2). The reaction was tolerant to the electronic nature of aryl aldehydes as both electron-donating and withdrawing substituted aldehydes worked well to deliver the corresponding products in good to excellent yields (3a-3g). Strongly electron-withdrawing substituents like –NO2 and –CN had a negative impact on the reaction, as the yield of the corresponding products decreased significantly, irrespective of the position of the substituents (3h-3j). The steric factor has negligible effect on this transformation, as 2-substituted aryl aldehydes gave their corresponding products in good yields. For instance, 2-F, 2-Cl, 2-Br benzaldehydes gave 78%, 80% and 81% of the corresponding amides respectively (3k-3m). In addition, hetero-aromatic aldehydes such as thiophene-2-carboxaldehyde, furan-2-carbaldehyde and pyridine-2-carboxaldehyde gave the corresponding amides in excellent yields (3n-3p). Gratifyingly, when the reaction was performed with aliphatic aldehydes like cyclohexanecarbaldehyde and n-butyraldehyde the reaction proceeded to give products with 76% and 42% yields respectively (Entries 3q-3r).

Table 3. Scope of aminopyridines for the oxidative amidation with benzaldehyde.[a]

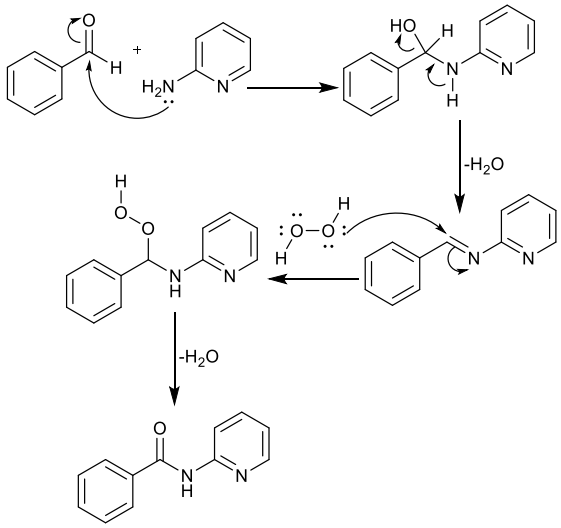


[a]Reaction Conditions: Benzaldehyde (1.0 mmol), aminopyridine (1.0 mmol), oxidant (3 equiv.), solvent (2 mL), 80 °C, 4 h, Isolated yield.

Next, we explored the scope and limitations of this oxidative amidation process for various substituted aminopyridines with benzaldehyde as shown in table 3. Irrespective of the electronic nature of the substituents in 2-aminopyridine, the yield ranges from good to excellent (**3s**-**3x**). When a strong electron-withdrawing nitro group is present in the 5th position, the yield of the product decreased drastically to 55% (**3y**). Even dichloro substituent in 2-aminopyridine gave the corresponding amide in excellent yield of 82% (entry **3z**). Interestingly, when 3-aminopyridine and 4-aminopyridine were taken as the coupling partners, respective amides were obtained in good yields of 78% and 79% respectively (**3aa**, **3ab**). When 2-aminopyrazine was taken as the amine counterpart, the corresponding amide was obtained in a moderate yield of 62% (**3ac**).



Scheme 2. Control experiments for oxidative amidation



Scheme 3. Plausible mechanism for the oxidative amidation

In order to arrive at the plausible reaction mechanism, we have done several background experiments. The reaction did not proceed when benzoic acid was taken as the starting material, instead of benzaldehyde along with 2-aminopyridine under the optimized reaction conditions (Scheme 2). This reaction confirms that acid cannot be the reaction intermediate. When benzaldehyde was treated with 2-aminopyridine, we could observe imine by TLC. To this imine, when oxidant was added, the desired amide was obtained in good yields. Moreover, when the reaction was carried out in absence of oxidant, the reaction failed indicating that the oxidant is essential for this amidation process. Based on the above observations, we propose the mechanism as shown in scheme 3. Addition of amine across the carbonyl group is a well-established process both in

solution[19a] and vapour phase.[19b-d] This is similar to the one proposed by Wolf *et al*. where amidation of aldehydes with secondary amines were performed in presence of TBHP as the oxidant.[8] The hemiaminal intermediate **I1** water to generate the imine **I2** followed by the addition of H_2O_2 to the imine giving the hydroperoxide **I3**.[11] Removal of water from the hydroperoxide **I3** afforded the required amide.

Conclusions

In conclusion, aqueous H_2O_2, a green oxidant, without any additive or metal catalyst in environmentally benign water medium, has been utilized for the efficient synthesis of *N*-(pyridinyl)benzamide from aldehydes and aminopyridines. The scope of the reaction includes heterocyclic aldehydes and sterically hindered 2-substituted aldehydes. Apart from 2-aminopyridine and it's derivatives, the reaction proceeded with 3-aminopyridine and 4-aminopyridine also as coupling partners.

Acknowledgements

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