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To Explore Cu-Catalyzed Oxidative Amidation of Cinnamic Acids / Arylacetic Acids with 2-Amines

Jasmin Haider Bagwan[1], Dr. Arun Sharma[2]

[1]PhD Scholar, Department of Chemistry, Sunrise University, Alwar, Rajasthan

[2]Professor, Department of Chemistry, Sunrise University, Alwar, Rajasthan

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Address for Correspondence: Jasmin Haider Bagwan

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Abstract

When it comes to pharmaceutical components in particular, air-and moisture-sensitive organometallic species might be problematic due to their inherent contamination, functional group compatibility issues, and stringent reaction conditions. The method's synthetic value was further shown by conducting a gram scale reaction under standard circumstances using cinnamic acid and morpholine. This reaction yielded the intended product, 1-morpholino-2-phenylethane-1,2-dione (3a), in 51% yield. The reaction's viability was assessed by meticulously manipulating a model reaction involving isatin and (E)-3-(benzylamino)-3-(methylthio)-1-phenylprop-2-en-1-one, changing variables including catalyst, solvent, temperature, and molar concentration of the reactants. The results of the control tests, the products' isolation, and the current literature are used to construct a plausible mechanism.

Keywords: Cinnamic, Acids, Amines, Synthesis And A-Ketoamides

Introduction

In organic chemistry, where many industrial processes involve harmful chemicals and solvents, the importance of greener reactions cannot be overstated. These processes cause significant environmental damage. The term "green techniques" is used to describe a variety of practices in organic chemistry, such as reactions that activate C-H bonds, bio- and asymmetric synthesis, reactions that use water or other green solvents (such as ionic liquids) or none at all, reactions that are assisted by microwaves, ultrasounds, or ultraviolet light, and the use of flow reactors. The publication practices of the Green Royal Society and two crucial.

Many natural products, bio-active compounds, and medications, including those that fight against HIV, tumors, inflammatory bowel disease (IBD), bacteria, immunosuppressants, and enzyme inhibitors, include α-ketoamides as essential structural motifs. In addition to being synthons and useful intermediates in many functional group transformations, they also play an important role in complete synthesis. Various approaches have been investigated for the production of α-ketoamides, including transition-metal catalysts derived from Pd, Cu, Ag, Au, and Fe, and metal-free catalysts, particularly those based on iodine, due to its possible importance.

Different methods for synthesizing α-ketoamides have been developed in the last few years. Two of the most popular

catalytic ways for α-ketoamide synthesis are 1) oxidative amidation utilizing molecular oxygen (O2) or air as a terminal oxidant and 2) double carbonylation/CO insertion by employing CO as a direct source of carbonyl functionality. Jiao and colleagues detailed a method for synthesizing α-ketoamides utilizing aromatic primary amines, which involves a Cu-catalyzed oxidative amidation-diketonization process of terminal alkynes. They activated the reaction with dioxygen in an ambient setting using molecular oxygen as an oxidant.

Literature Review

Luigi Vaccaro et.al (2020) An important area for the research and use of novel solvents to enhance existing transformations or find new ones is organic chemistry, which is crucial in the field of sustainable development, which relies heavily on chemistry. A crucial tool for contemporary organic chemistry, recoverable catalysts are essential for accessing successful green synthesis methods. At last, technologies like flow chemistry may make the most of the attempts to limit energy consumption and waste during synthetic operations. The minireview provides an inside look at the work my group has done in the previous decade in the field of organic chemistry, focusing on how we've used flow reactors, heterogeneous catalysis, and safer/recoverable solvents to get closer to greener practices.

Clément Michelin et.al (2018) One effective tool for organic synthesis is photocatalytic reactions. Complex nitrogen-containing heterocycles have been synthesized by photooxygenation of furan derivatives. When paired with photoredox processes, enzyme catalyzed asymmetric oxidations become simpler. To create products with biological activity, it is necessary to synthesize fluoroorganic molecules. For this reason, the photoredox catalytic trifluoromethylation of aromatic and, in particular, heteroaromatic compounds is a promising process with potential medicinal uses.

Claudia Espro et.al (2021) Sustainable organic process development is now within reach, thanks to new opportunities made possible by the expanding field of mechanochemistry. From procedures developed in the lab to their implementation in real-world industries, this contribution details the most current developments in this field. Additionally, new developments in in-situ characterization studies and mechanochemical methods have been covered. Many technologies have been studied and created with the goal of scaling up their uses. These include high-throughput reaction platforms and twin-screw extrusion, which can combine heat and continuous-flow mechanochemical conditions. It should be noted that mechanochemistry is a very promising method that has many untapped potentials.

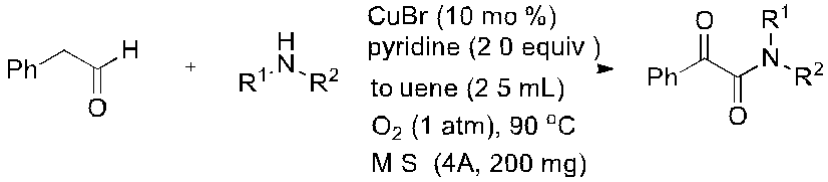
Lars-Erik Meyer et.al (2021) The study of biocatalysis by light is an emerging and young discipline. Given the exponential growth in the field's output, this review focuses on articles highlighting breakthroughs in photobiocatalysis that have appeared in the last two years. We provide a quick overview of the subject and compile a list of the majority of the review articles that have so far been published. After that, we quickly outline new findings in photobiocatalytic cascades and in enzymes that are strictly light-dependent, and we focus on the most intriguing and important studies in the area of in vitro photobiocatalysis. The last section, "Conclusions and Future Perspectives," lays out our plans for the next decade.

Piera De Santis et.al (2020) There has been a meteoric rise in research into enzymes in continuously run flow reactors, according to the biocatalysis community. The idea of merging the two fields' strengths—the micro-scale improved mass transfer and resource efficiency in flow

chemistry and the outstanding selectivities in biocatalysis—was what sparked this considerable interest. Biocatalysis in continuously operating systems has seen significant advancements in the last few years, from 2018 to September 2020, which are covered in this analysis. Our primary emphasis is on enzyme-catalyzed reactions as we provide a concise overview of the basics of continuously running reactors. We focused on the potential future developments in this important new field of technology, which includes everything from digitization to process analytical tools.

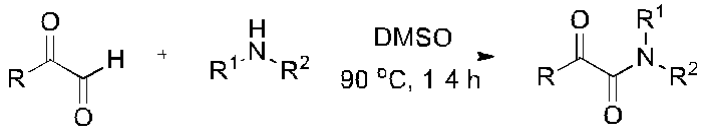
Material Method

A method for producing α-ketoamides from aryl acetaldehydes and anilines by aerobic oxidation with CuBr was devised by Jiao et al. One NH bond, two (sp3) C-H bonds, and one (sp2) C-H bond are all broken during the reaction.



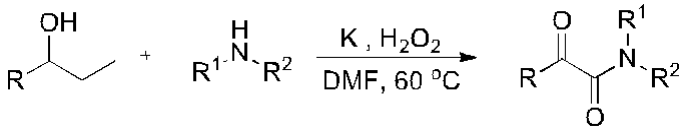
Scheme 1 Aerobic oxidative coupling of aryl acetaldehydes with amines.

A metal-free oxidative amidation of 2-oxoaldehydes with amines was described by Vishwakarma and colleagues in 2014. Dimethyl sulfoxide (DMSO) is an oxidant and a solvent all in one. In a DMSO environment, the carbonyl group of oxo-aldehydes directs and stabilizes the production of iminium ions.



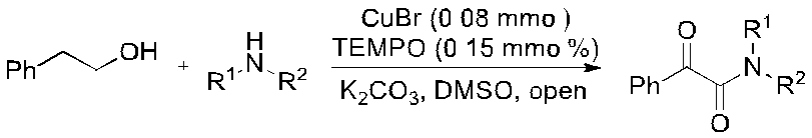
Scheme 2 Oxidative amidation of 2-oxoaldehydes and amines.

Guo et al. (2016) showed that by direct oxidative coupling between 2□ benzylic alcohols and amines utilizing H2O2 as an oxidant, a continuous-flow method may be used to synthesize α-ketoamides and α-amino ketones



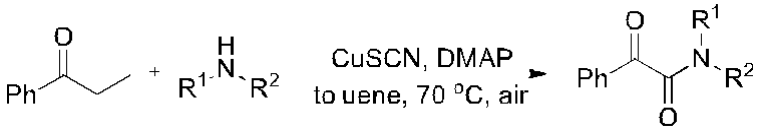
Scheme 3 Synthesis of *α*-ketoamides and *α*-amino ketones.

The same group also discovered in the same year the tandem sp3 C-H aerobic oxidation and the amination of phenethyl alcohol with primary and secondary amines. α-ketoamides were synthesized by four Csp3-H and one N-H bond cleavages brought about by the combination of copper and TEMPO.



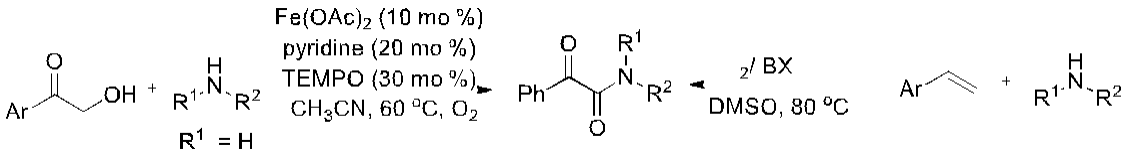
Scheme 4 Aerobic oxidation and amination of phenethyl alcohol with amines.

In 2017, Guo et al. once again demonstrated a method to obtain α-ketoamides by selectively oxidatively cleaving C(α)-C(β) bonds of simple saturated aryl ketones and then amidating them. The reaction's molecular oxygen serves as a final oxidant. The four-membered intermediate is produced when the intermediate enamine combines with the peroxide that is created in the medium. The α-ketoamide is then obtained upon breakage of the C-C and O-O bonds.



Scheme 5 Oxidative C(*α*)–C(*β*) bond cleavage and amidation of saturated aryl ketones.

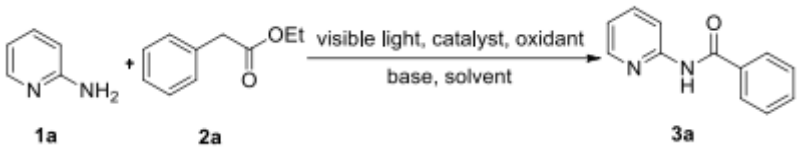
Sekar et al. devised a method for synthesizing α-ketoamides utilizing 2-hydroxyacetophenones and amines in an aerobic domino alcohol oxidation/oxidative cross-dehydrogenative coupling process that is catalyzed by iron-TEMPO. the α-ketoamides were synthesized by the same group utilizing a mix of terminal alkenes (styrenes) and amines in an I2/2-iodoxybenzoic acid (IBX)/DMSO solution.



Scheme 6 Sekar's work for the synthesis of *α*-ketoamides.

Results and Discussion

Table 1 Optimization of the reaction conditions.



Entry	Catalyst	Oxidant	Base	Solvent	Yield (%)[b]
1	CuI	Air	K2CO3	DMSO	46
2	CuI	Air	K2CO3	DMF	Nil
3	CuI	Air	K2CO3	DCE	Nil
4	CuI	Air	K2CO3	CH3CN	71[c]
5	CuI	Air	K2CO3	CH3CN	Nil[d]
6	-	Air	K2CO3	CH3CN	Nil
7	CuI	TBHP	K2CO3	CH3CN	20
8	CuI	K2S2O8	K2CO3	CH3CN	Trace
9	CuCl	Air	K2CO3	CH3CN	Trace
10	CuBr	Air	K2CO3	CH3CN	63
11	Cu2O	Air	K2CO3	CH3CN	61
12	CuI	Air	K3PO4	CH3CN	68
13	CuI	Air	Et3N	CH3CN	Nil
14	CuI	Air	*t*-BuOK	CH3CN	Nil
15	eosin Y	Air	K2CO3	CH3CN	Nil
16	CuI	Air	K2CO3	CH3CN	Trace[e]
17	CuI	Air	K2CO3	CH3CN	52[f]
18	CuI	Air	K2CO3	CH3CN	48[g]

The reaction conditions include 1a (1.0 mmol), 2a (1.0 mmol), a catalyst (20 mol%), a base (2.0 equiv), a solvent (1.0 mL), white CFL (15W), and 36 hours at room temperature. [b] ROI calculation after column chromatography. [c] A similar yield was attained when molecular oxygen was present. In the absence of visible light. [e] Utilizing a green light-emitting diode with a wavelength of 530 nanometers. "f" by the use of a 470 nm blue light-emitting diode. [g] Once a day at 80 ºC.

By manipulating the parameters of a model reaction involving 2-aminopyridine (1a) and ethyl phenylacetate (2a), we were able to determine the optimal reaction conditions. In Table 1, you can observe the outcomes.

Starting the reaction with CuI and K2CO3 in DMSO in an open atmosphere under visible light led to the synthesis of the product N-(pyridin-2-yl) benzamide (3a) with a yield of 46% Table 1, entry 4 shows that product yield increased by 71% when acetonitrile was used; however, entry 2 and entry 3 show that product yield was unaffected when DMF or DCE were substituted for DMSO. As can be seen from entries 5 and 6 of Table 1, the product was not produced at all when a copper catalyst and visible light were not utilized. Entries 7 and 8 of Table 1 reveal that TBHP and K2S2O8 were also tried as reaction air substitutes, but they did not provide any useful findings. By substituting CuI with CuCl, CuBr, or Cu2O, or any of the other Cu(I) salts, performance remained unchanged.

Table 1, entries 12–14 shows that all inorganic and organic bases except K3PO4 showed performance similar to that of K2CO3. Similarly, replacing the Cu catalyst with eosin Y had no impact either. Table 1, entries 16 and 17, shows that the effects of light of various wavelengths were also studied. These included 530 nm green LED and 470 nm blue LED. Blue LED could provide a considerable quantity of conversion, but green LED was completely useless. A product yield of 48% was achieved when the reaction was confirmed under heat conditions. After that, we tested a range of catalyst loading and solvent concentration values to find the optimal combination; 20 mol% CuI and 1 mL CH3CN were the winners. Optimal results were obtained under visible light at room temperature by combining 1a and 2a in equal parts with 20 mol% CuI and K2CO3 in acetonitrile.

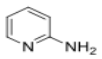
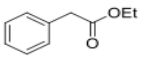
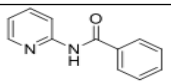
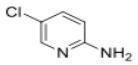
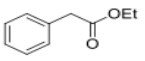
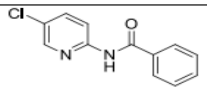
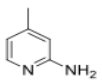
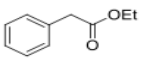
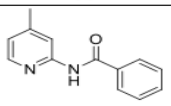
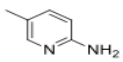
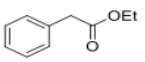
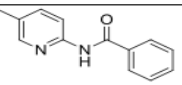
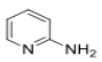
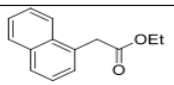
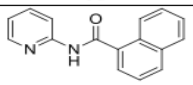
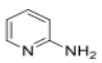
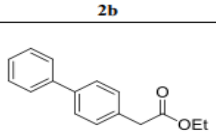
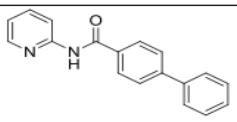
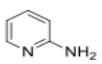
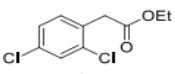
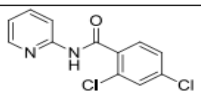
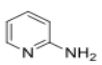
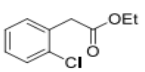
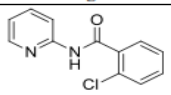
Table 2 shows the results of a second investigation that was run under ideal conditions to find out how wide and flexible the response was. A variety of aminopyridines such as pyridin-2-amine (1a), 5-chloropyridin-2-amine (1b), 4-methylp yridin-2-amine (1c), 5-methylp yridin-2-amine (1d) and 6-methylpyridin-2- amine (1e) were made to react with different ethyl arylacetates viz. ethyl 2 phenylacetate (2a), ethyl 2-(naphthalen-1-yl)acetate (2b), ethyl 2-([1,1'-biphenyl]-4-yl)acetate (2c), ethyl 2-(2,4-dichlor ophenyl)acetate (2d), ethyl 2-(2-chlorophenyl)acetate (2e), ethyl 2-(4-fluorophenyl)acetate (2f), ethyl 2-(4-chlorophenyl)acetate (2g), ethyl 2-(thiophen-3-yl) acetate (2h), ethyl 2-(o-tolyl)acetate (2i), ethyl 2-(p-tolyl)acetate (2j), ethyl 2-(4-bromophenyl)acetate (2k) and ethyl 2-(3- nitrophenyl)acetate (2l) to construct a number of products namely N-(pyridin-2- yl)benzamide (3a), N-(5-chloropyridin-2-yl)benzamide (3b), 1-Naphthamide (3e), N-(pyridin-2-yl)}the chemical name for 1,1'-bisphenol-4-carboxamide (3f), 2,4-dichloro-N- (pyridin -2-yl) benzamide (3g), 2-chloro-N-(pyridin-2-yl)benzamide (3h), 4-fluoro-N-(pyridin-2-yl)benzamide (3i), 4-chloro-N-(pyridin-2-yl)benzamide (3j), N-(pyridin-2- yl)thiophene-3-carboxamide (3k), 2-methyl-N-(4-methylpyridin-2-yl) benzamide (3l), 4- methyl-N-(4-methyl pyridin-2-yl)benzamide (3m), 4-bromo-N-(6-methylpyridin-2- yl)benzamide (3n), 2,4-dichloro-N-(4-methylpyridin-2-

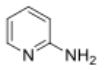
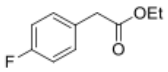
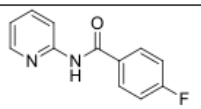
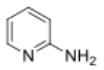
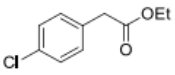
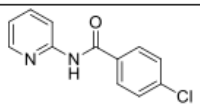
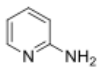
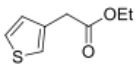
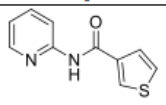
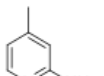
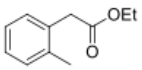
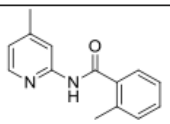
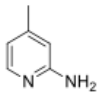
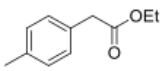
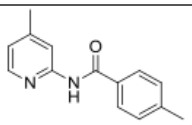
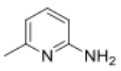
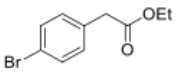
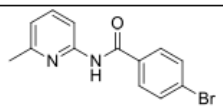
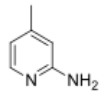
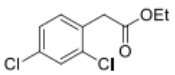
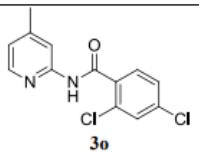
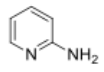
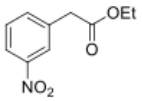
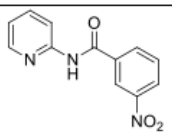
yl)benzamide (3o), 3-nitro-N- (pyridin-2-yl)benzamide (3p) in fairly high yields.

The 3b product, which yielded 56% from the 3-chloro-2-amiopyridine and ethyl phenylacetate reaction, was much lower than the 3a product, which yielded 71% from the 2-aminopyridine and ethyl phenylacetate reaction. The product yield was unaffected by the presence of a methyl substituent at positions 4 or 5, as shown in 3c and 3d, Table 2, entries 3 and 4. Entries 5 and 6 of Table 2 demonstrate that 2-aminopyridine reacted well with ethyl naphthyl acetate to produce 3e, and with ethyl biphenyl acetate to produce 3f. Using several halo-substituted ethyl arylacetates, reacting with 2-aminopyridine also resulted in the desired products 3g-3j in quite high yields.

Table 2, entry 11 shows that the ester with a heterocyclic core also achieved a 60% yield and successfully formed 3k in the process. Table 2, entries 12 and 13, shows that the product yields were consistently enhanced when both reaction partners had a methyl substituent (3l: 70% & 3m: 72%). Table 2, entries 14 and 15, shows that the reaction between methyl substituted 2-aminopyridine and halo-substituted esters was remained mild, giving 3n and 3o. Although 1a could react with esters that included nitro substituents, the resultant yield was much lower. In the reaction with 1a, ethyl heptanoate completely bombed at making the desired result.

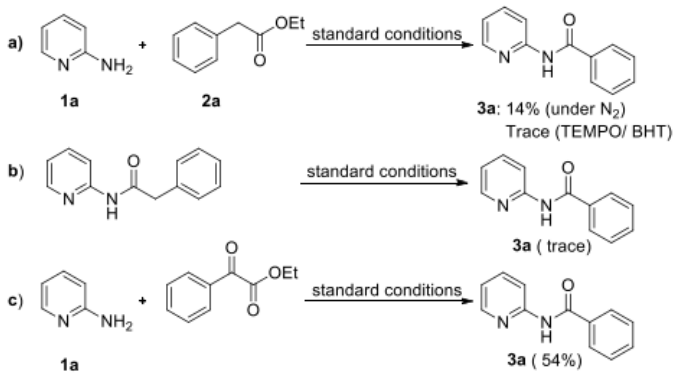
Table 2 The scope of the reaction using 1 and 2 under optimum conditions. A

Entry	Aminopyridine (1)	Ethyl arylacetate (2)	Product (3)	Yield (%)[b]
1	 1a	 2a	 3a	71
2	 1b	 2a	 3b	56
3	 1c	 2a	 3c	67
4	 1d	 2a	 3d	72
5	 1a	 2b	 3e	61
6	 1a	 2c	 3f	60
7	 1a	 2d	 3g	65
8	 1a	 2e	 3h	67

9	 **1a**	 **2f**	 **3i**	66
10	 **1a**	 **2g**	 **3j**	64
11	 **1a**	 **2h**	 **3k**	60
12	 **1c**	 **2i**	 **3l**	70
13	 **1c**	 **2j**	 **3m**	72
14	 **1e**	 **2k**	 **3n**	65
15	 **1c**	 **2d**	 **3o**	59
16	 **1a**	 **2l**	 **3p**	21

The reaction variables are as follows: 1 (1.0 mmol), 2 (1.0 mmol), CuI (20 mol%), K2CO3 (2.0 equiv), CH3CN (1.0 mL), white CFL (15W), and 36 hours of room temperature exposure to the air. [a] In Profitability following column chromatography.

So that we could learn more about the reaction mechanism, we ran a few of control experiments. Although the crucial role of aerobic conditions was confirmed by studying the reaction in a nitrogen environment, the product yield was still decreased by 14% Figure 1, equation (a) shows that the product couldn't be made in the usual reaction when radical scavengers like TEMPO or BHT were present. Schema 4.13, equation (b) demonstrates that this 2-phenyl-N-pyridin-2-yl-acetamide is not suitable for use as an intermediate since, when subjected to the given conditions, it failed to generate the desired product 3a. equation c, the product of interest was generated in 54% yield during the reaction of 1a with ethyl oxophenylacetate, which implies that it may serve as an intermediary.



Scheme 7 Control experiments.

The results of control trials, previous research (26–31, 42–43, 44–49), and product separation were used to build a plausible process, as shown in Figure 1. Under this process, 2a is subjected to CuI radiation to generate an activated intermediate I. Subsequently, when this intermediate is exposed to oxygen, it goes through a cascade of reactions that result in the synthesis of hydroperoxo species (III). After species III is eliminated, it produces ethyl oxophenylacetate (IV). To create species VI in an aerobic setting, react IV with 1a when a base is present to generate the imine V. Then, species VI is formed by reacting IV with copper. In order to get the required product, species VII, VIII, and IX sequentially remove CO2 via O-O bond breakage, cyclization by removing OEt, and H abstraction from 2a, respectively. 3a.

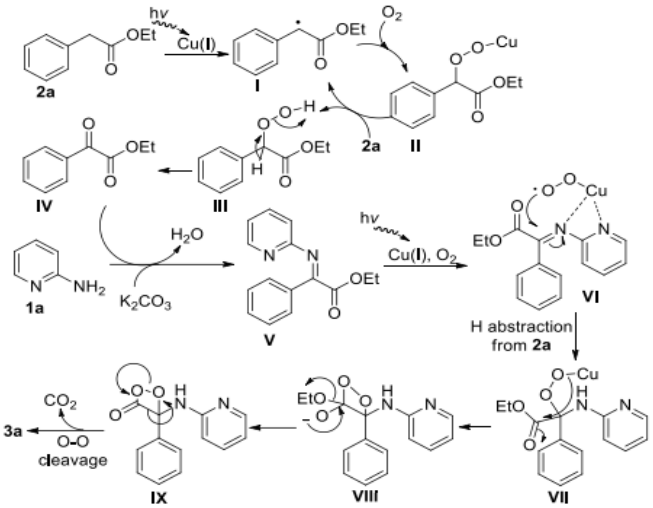


Figure 1 Plausible mechanism.

With visible light and Cu(I) as a catalyst, our findings demonstrate that ethyl arylacetates and 2-aminopyridines may be amidated aerobically at room temperature. A series of steps leading to N-(pyridin-2-yl) benzamides are as follows: ethyl arylacetates undergo benzylic CH2 oxidation, imine synthesis, and oxidative decarbethoxylation.

Conclusion

To discover safer and more environmentally friendly alternatives to well-known coupling reactions, it is helpful to choose the reacting partners and catalysts correctly. The use of reactive intermediates allows for the production of crosscoupling products, which may include radicals, carbenes, carbocations,

radical cations, anion, etc. Carboxylic acids, esters, amines, heterocylic compounds, and other similar substrates have been studied extensively due to their high propensity to produce reactive intermediates in mild environments. Another promising alternative to the current ones is the production of reactive intermediates using a variety of metal-free catalysts. this process involves a novel and easy way to make α-ketoamides by oxidative amidation of easily accessible and stable cinnamic acids or arylacetic acids with 2□ amines in an open-air setting using Cu (OAc)2. The method makes use of oxidative amidation of cinnamic acids and in situ decarboxylation.

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