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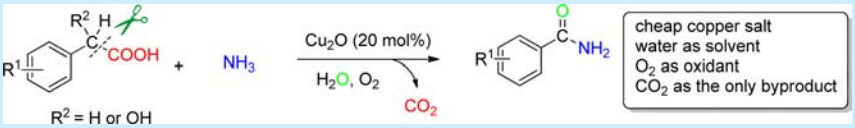
Synthesis of Primary Amides via Copper-Catalyzed Aerobic Decarboxylative Ammoxidation of Phenylacetic Acids and α-Hydroxyphenylacetic Acids with Ammonia in Water

Qiuling Song,* Qiang Feng, and Kai Yang

Institute of Next Generation Matter Transformation, College of Chemical Engineering at Huaqiao University, 668 Jimei Boulevard, Xiamen, Fujian, 361021, P. R. China

Supporting Information

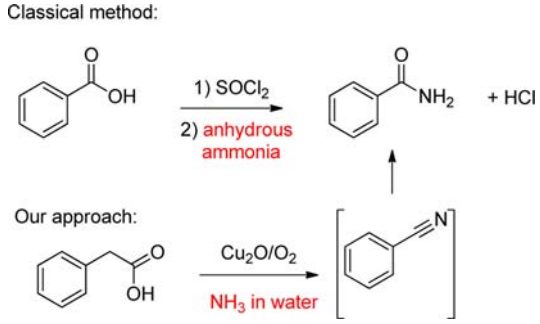


ABSTRACT: A Cu_2O-catalyzed aerobic oxidative decarboxylative ammoxidation to primary benzamides from phenylacetic acids and α-hydroxyphenylacetic acids is developed. A variety of primary benzamides could be prepared smoothly, in good to excellent yields, by means of a one-pot domino protocol combining decarboxylation, dioxygen activation, oxidative C−H bond functionalization, and amidation reactions.

Aromatic primary amides are regarded as an important class of compounds in organic synthesis, pharmaceutical chemistry, and chemical engineering.[1−3] They are also present in numerous biologically active molecules.[4] In synthetic chemistry, primary amides are very good functional groups which can be easily transformed into nitriles, primary amines, and heterocycles. For these reasons, numerous methodologies have been developed for their synthesis. Some examples are the ammonolysis of carboxylic acids,[5,6] the rearrangement of benzaldoximes,[7] the palladium-catalyzed carbonylation of organo halides with ammonia,[8] the direct oxidation of benzyl amines[9] or benzyl alcohol[10] to the corresponding benzamides, and the hydration of the corresponding nitriles.[11−13] Of these methods, the ammonolysis of activated carboxylic acid species is still the traditional method for synthesis of primary amides.[5,6] However, this procedure requires preactivation of the free carboxylic acid with stoichiometric activating reagents, and corrosive byproducts are often generated during the reaction (Scheme 1). Thus, the development of greener and more efficient methods to prepare amides from readily available carboxylic acids is still a big challenge for synthetic organic chemistry.

Currently, transition-metal-catalyzed decarboxylative couplings have attracted much attention due to readily accessible starting materials, simple operation, and clean byproduct (CO_2 as the only byproduct). Among the decarboxylative couplings reactions, palladium-catalyzed methods are well studied and provided novel protocols for C−C or C−heteroatom bond formation.[14−19] However, those palladium-mediated or catalyzed methods suffer from some drawbacks: (a) palladium is quite expensive; (b) air or moisture-sensitive, and very expensive, bulky phosphines are always required for the success of the reactions; (c) other additives, such as stoichiometric silver salts, are frequently encountered in the reactions. In light of the recent demands for environmentally benign and economically attractive organic syntheses, much cheaper copper salts have many advantages and remarkable progress has been made with copper-catalyzed coupling reactions;[20−22] yet copper-only catalyzed decarboxylative coupling reactions[21,23−25] are relatively rare compared to well-developed palladium-catalyzed ones.

Scheme 1. Synthesis of Primary Amides from Carboxylic Acids



Molecular oxygen is an ideal terminal oxidant for oxygenation, because of its abundance, negligible cost, and high atom efficiency. To the best of our knowledge, there is no known reaction that encompasses the decarboxylation of $C(sp^3)$ with simultaneous formation of $C(sp^2)(C{=}O)-N$ bonds via copper-catalysis with O_2 as the sole terminal oxidant. As part of our ongoing research into the development of oxidative decarboxylation reactions at $C(sp^3)$,[26] we herein report a novel aerobic decarboxylative ammoxidation of readily available phenylacetic

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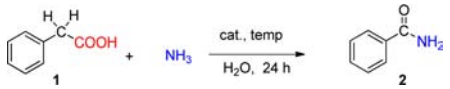
acids and α-hydroxyphenylacetic acids to primary amides in aqueous ammonia solution in ligand-, acid- or base-free patterns.

Our initial investigation commenced with phenylacetic acid (**1**) in aqueous ammonia in the presence of $Cu(OAc)_2$ at 130 °C under oxygen atmosphere. To our delight, benzamide (**2**) was obtained in 38% isolated yield (Table 1, entry 1). Catalyst

Table 1. Optimization of the Reaction Conditions[a]



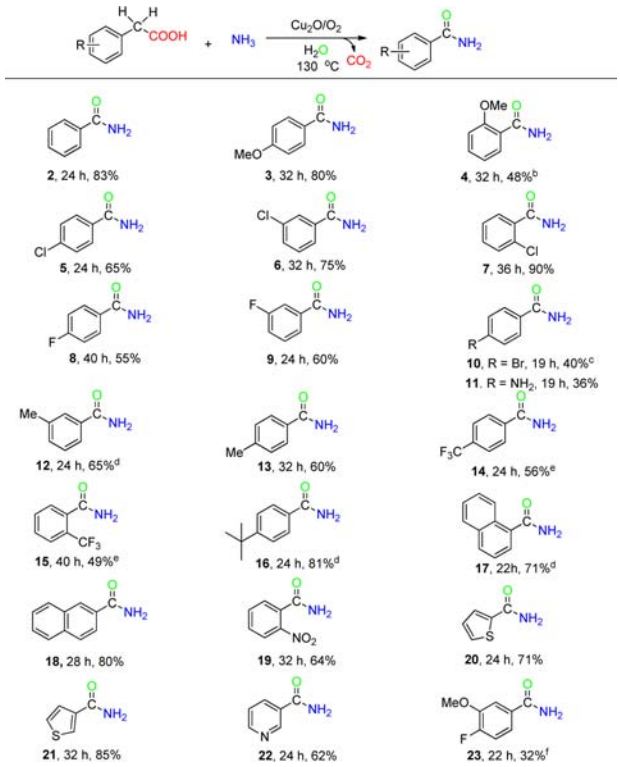
entry	catalyst	oxidant	solvent	temp (°C)	yield[b] (%)
1	$Cu(OAc)_2$ (10 mol %)	O_2		130	11
2	$Cu(OAc)_2$ (20 mol %)	O_2		130	38
3	$Cu(TFA)_2$ (20 mol %)	O_2		130	trace
4	$Cu(OTf)_2$ (20 mol %)	O_2		130	trace
5	$CuCl_2$ (20 mol %)	O_2		130	32
6	CuBr (20 mol %)	O_2		130	26
7	$CuSO_4$ (20 mol %)	O_2		130	47
8	**Cu_2O (20 mol %)**	**O_2**		**130**	**83**
9	CuO (20 mol %)	O_2		130	47
10	$Fe(acac)_2$ (20 mol %)	O_2		130	0
11	$FeCl_3$ (20 mol %)	O_2		130	0
12	Cu_2O (20 mol %)	air		130	9
13	Cu_2O (20 mol %)	N_2		130	0
14	Cu_2O (20 mol %)	O_2		100	20
15	Cu_2O (20 mol %)	O_2		120	80
16	Cu_2O (20 mol %)	O_2	DMF	130	63
17	Cu_2O (20 mol %)	O_2	DMSO	130	30
18	Cu_2O(10 mol %)	O_2		130	52
19	Cu_2O (20 mol %)	TBHP		130	28
20	Cu_2O (20 mol %)	DTBP		130	31
21		O_2		130	0

[a]Reaction conditions: phenyl acetic acid (0.5 mmol), catalyst, ammonia in aqueous water (1.5 mL) in a sealed tube under corresponding atmosphere. [b]Isolated yield.

screening showed that Cu_2O gave the best isolated yield of the desired product (83%, Table 1, entry 8). Notably, CuO only gave 47% of desired product even though it was considered that Cu_2O should be oxidized into CuO under oxidative conditions. Further investigation indicated that oxygen plays a crucial role in the reaction (Table 1, entries 1, 12, 13, 19, and 20). This transformation is sensitive to temperature: when the temperature was dropped to 120 and 100 °C, the isolated yields dropped to 80% and 20%, respectively (Table 1, entries 14 and 15). Solvent screening showed water to be the best solvent, and addition of other solvents gave lower yields of the desired products (Table 1, entries 16 and 17). When catalyst loading was dropped to 10 mol %, only 52% of the desired product was afforded (Table 1, entry 18). Without copper catalyst, there is no reaction at all (Table 1, entry 21), which demonstrates that copper is vital for the success of the reaction.

A variety of substituted phenylacetic acids were subjected to the optimized conditions to evaluate the scope of the decarboxylative ammonoxidation reaction. As shown in Scheme 2, phenylacetic acids with both electron-rich and electron-deficient substituents on the aromatic ring could be smoothly converted into the desired products. The position of the substituents on the aromatic rings had some effect on yields (Scheme 2, **3**−**4**, **5**−**7**, **8**−**9**, and **14**−**15**), with *ortho*-substitution

Scheme 2. Copper-Catalyzed Aerobic Oxidative Decarboxylative Ammoxidation of Phenylacetic Acids to Benzamides[a]



[a]Reaction conditions: phenylacetic acid (0.5 mmol), Cu_2O (20 mol %), ammonia in water (1.5 mL), O_2. [b]This reaction was carried out at 150 °C. [c]This reaction was carried out at 95 °C. [d]These reactions were carried out at 140 °C. [e]This reaction was carried out at 100 °C. [f]This reaction was carried out at 110 °C.

usually giving lower yields of the benzamides when compared to *meta*- and *para*-substitution, probably as a result of steric hindrance. It is noteworthy that most halo-substituted aryl groups survived well, leading to halo-substituted aromatic carboxamides which could be used for further transformations (Scheme 2, **5**−**9**). In addition, 1-naphthylacetic acid and 2-naphthylacetic acid also reacted well to give the corresponding naphthyl carboxamides in 71% and 80% yields (Scheme 2, **17** and **18**). Nitro groups also survived under the standard conditions (Scheme 2, **19**), and heteroaromatic acetic acids were transformed well into corresponding primary amides (Scheme 2, **20**, **21**, and **22**).

Inspired by the above results, we applied the same conditions to α-hydroxyphenylacetic acids. To our delight, when α-hydroxyphenylacetic acid (**24**) was treated with aqueous ammonia under standard conditions, benzamide was obtained in 58% isolated yield (Scheme 3, entry 1). Without further optimization, the standard conditions were applied to various α-hydroxyphenylacetic acids to explore the tolerance of the reaction, and the results are shown in Scheme 3. The reaction worked well with diverse α-hydroxyphenylacetic acids to give the corresponding benzamides in 45−72% isolated yields.

In order to understand the reaction mechanisms, several control experiments were performed. Since the reaction involves oxygen, radical trapping experiment was conducted by employing 2,2,6,6-tetramethyl-1-piperidinyloxy (BHT) with phenylacetic acid. The result showed that the reaction was totally

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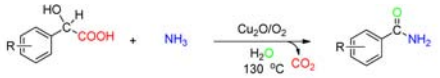
Scheme 3. Copper-Catalyzed Aerobic Oxidative Decarboxylative Ammoxidation of α-Hydroxyphenylacetic Acids to Benzamides[a]

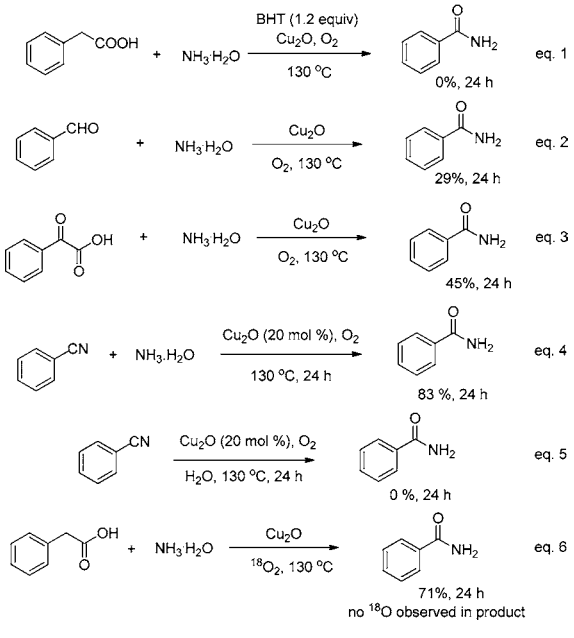


entry	starting materials	products	yield (%)[b]
1	**24**	**2**	**2**, 24 h, 65%
2	**25**	**3**	**3**, 24 h, 70%
3	**26**	**5**	**5**, 24 h, 60%
4	**27**	**6**	**6**, 24 h, 45%
5	**28**	**8**	**8**, 36 h, 50%
6	**29**	**33**	**35**, 24 h, 63%
7	**30**	**9**	**9**, 24 h, 60%
8	**31**	**14**	**14**, 24 h, 67%
9	**32**	**34**	**36**, 24 h, 72%

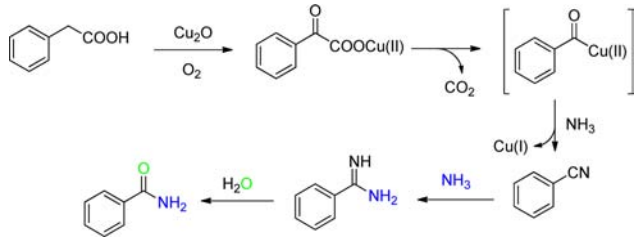
[a]Reaction conditions: 1 (0.5 mmol), Cu_2O (20 mol %), ammonia (1.5 mL), O_2. [b]Isolated yield.

inhibited by BHT (Scheme 4, eq 1), so the reaction should be a radical pathway. The reactions of benzyl alcohol, benzaldehyde, benzoic acid, and 2-oxo-2-phenylacetic acid with ammonia under standard conditions were also explored. Both benzyl alcohol and benzoic acid afforded no desired benzamide at all (Supporting Information , eqs S1 and S2), showing that benzyl alcohol and benzoic acid are not intermediates for this reaction. However, benzaldehyde and 2-oxo-2-phenylacetic acid gave 29% and 45% of benzamide, respectively (Scheme 4, eq 2 and eq 3); when phenylacetic acid was directed heated at 130 °C without ammonia under standard conditions, 10% of benzaldehyde was obtained (Supporting Information, eq S3). Interestingly, during condition screening, we observed benzonitrile generated during the reaction. Benzonitrile was formed after 2 h of heating under the standard conditions with some starting material remaining, and 4 h later, the benzamide peak appeared upon GC analysis with the benzonitrile peak shrinking. After about 24 h, the benzamide peak is the major component and the benzonitrile peak almost completely disappeared. In order to verify whether benzonitrile is the key intermediate or not, two control experiments were employed: one is under the standard conditions (Scheme 4, eq 4) and another one is treated only in water (Scheme 4, eq 5). The former reaction gave 83% of the desired product, but the latter one gave no product at all. The experiments clearly showed that ammonolysis, not just hydrolysis, occurred in the conversion of benzonitrile to benzamide under the standard conditions and the two protons of amides in product were from ammonia, not water. In order to determine the oxygen source of the product, ^{18}O label experiment was also carried out under the standard conditions (Scheme 4, eq 6) with $^{18}O_2$. After purification, no ^{18}O was observed or detected in final product by LCMS, thus ruling out that the oxygen in product was from molecular oxygen; eventually, there is only one source that the oxygen can come from: the water. Based on all of the above control experiments, we gave a plausible reaction mechanism (Scheme 5): phenylacetic acid was oxidized into 2-oxo-2-phenylacetic acid and then decarboxylated to an organocopper species, which was in turn converted into benzonitrile, and after ammonolysis and hydrolysis of the benzonitrile, benzamide was obtained.

Scheme 4. Control Experiments



Scheme 5. Plausible Mechanism of Benzamide Formation from Phenylacetic Acid and Ammonia in H_2O



In conclusion, a Cu_2O-catalyzed decarboxylative ammoxidation of phenylacetic acids and α-hydroxyphenylacetic acids with ammonia in water has been developed. These reactions combined decarboxylation, dioxygen activation, oxidative C−H bond functionalization, and amidation reactions in a one-pot synthesis to generate primary aromatic amides in a practical and easy way.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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AUTHOR INFORMATION

Corresponding Author

*Email: qsong@hqu.edu.cn

Notes

The authors declare no competing financial interest.

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