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Amide Bond Formation via Aerobic Photooxidative Coupling of Aldehydes with Amines Catalyzed by a Riboflavin Derivative

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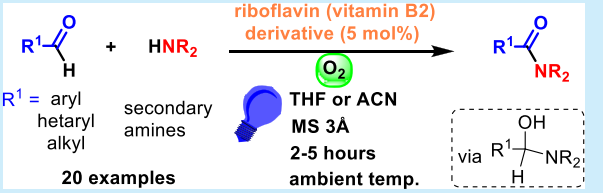
ABSTRACT: We report an effective, operationally simple, and environmentally friendly system for the synthesis of tertiary amides by the oxidative coupling of aromatic or aliphatic aldehydes with amines mediated by riboflavin tetraacetate (**RFTA**), an inexpensive organic photocatalyst, and visible light using oxygen as the sole oxidant. The method is based on the oxidative power of an excited flavin catalyst and the relatively low oxidation potential of the hemiaminal formed by amine to aldehyde addition.



Amides are not only the building blocks of natural peptides but also the key intermediates in the synthesis of polymers, agrochemicals, and 25% of modern pharmaceuticals.[1] To date, great efforts have been made to develop new and efficient approaches to amide formation as commonly used methods suffer from inherent disadvantages.[2] The direct thermal condensation of carboxylic acids and amines is the simplest method for the preparation of amides. However, this pathway is restricted to simple substrates because it requires harsh temperature conditions. Amides are traditionally synthesized from activated carboxylic acids or their derivatives and amines (Figure 1A),[2b,3] alternatively by the Beckmann rearrangement,[4] Schmidt reaction,[5] Staudinger ligation reaction,[6] and other reactions.[7] However, many of these strategies suffer from the production of large quantities of waste and byproducts. Thus, amide synthesis avoiding poor atom economy reagents remains one of the main challenges for organic chemistry.[8] As a consequence, new catalytic approaches for amide bond formation are of great interest from an industrial and academic point of view.[9]

As an alternative to the traditional methods, the transition-metal-catalyzed coupling of aldehydes with amines as well as metal-free oxidative amidation of aldehydes have achieved a breakthrough in amide synthesis (Figure 1B).[9−11] Nontoxic aldehydes are readily available and offer the possibility of starting the transformation from substrates other than carboxylic acids. Nevertheless, the majority of methods starting from aldehydes are characterized by disadvantages such as expensive catalysts/reagents, high temperatures, oxidizing agents other than oxygen, and, in some cases, low tolerance to secondary amines.[9] Recently, researchers directed their attention to photocatalytic procedures which usually offer mild and green alternatives to conventional approaches.[12] Among previously known photocatalytic systems for oxidative coupling of aldehydes and amines to amides are those requiring a stoichiometric additive as oxidant[13] or an electron- or oxygen-transfer reagent.[14] Alternatively, there are also simple methodologies using only a photocatalyst, like a phenazinium salt,[15] Rose Bengal[16] or anthraquinone,[17] and molecular oxygen (Figure 1C). Nevertheless, there are still limitations in substrate scope and effectiveness of photocatalytic aldehyde-amine couplings, namely, relatively long reaction times (20 h and more) and missing procedures for amides of aliphatic acids.

Derivatives of riboflavin (vitamin B2) are readily available blue-light-absorbing photocatalysts well suited to oxidative chemistry.[18] In addition to their ability to oxidize highly difficult substrates,[19] some flavins have been shown to provide delicate chemoselective oxidations.[20] In aprotic solvents, riboflavin tetraacetate (**RFTA**) was shown to behave as a two-electron oxidant in oxidation of 4-methoxybenzyl alcohol to benzaldehyde.[21] Considering all of the aforementioned factors and the photooxidation ability of flavin derivatives, we developed the first flavin-based photocatalytic approach to amide synthesis using **RFTA** as a catalyst. This system involves oxidative coupling of an aldehyde and a secondary amine using oxygen as a terminal oxidant and visible light. Amide formation proceeds under mild conditions without the need for an additional hydrogen/electron acceptor. **RFTA** is available in a single step from cheap commercially available riboflavin (Figure 1D).

The implementation of our strategy commenced with the model reaction of 4-chlorobenzaldehyde (**1a**) and piperidine (**2a**) in the presence of 5 mol % **RFTA** under blue light

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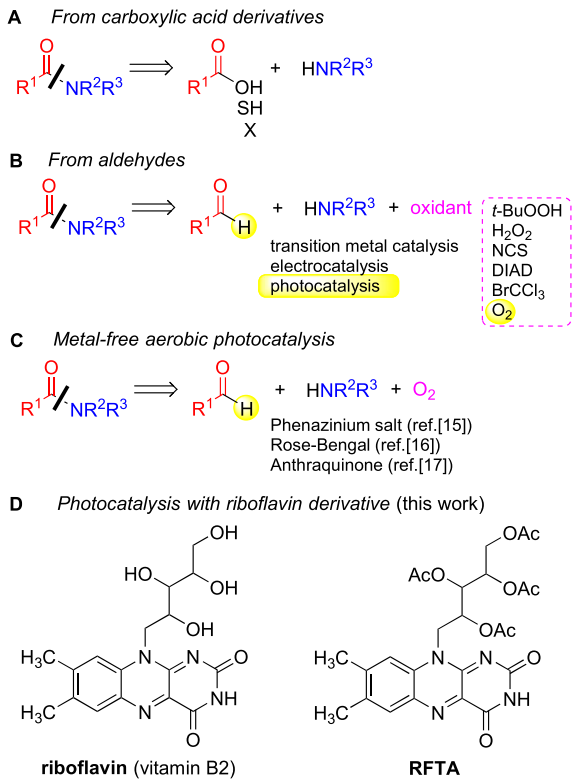
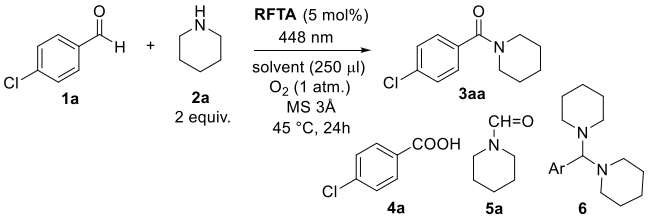


Figure 1. Development of amide synthesis using the standard approach starting from carboxylic acids (A) to novel methodologies starting from aldehydes (B) and those using aerobic metal-free photocatalysis (C,D).

irradiation. Molecular sieves (MS), known to decompose hydrogen peroxide (byproduct of flavin reoxidation, see Scheme 1D) to oxygen and water were used, thereby prolonging the lifetime of the flavin catalyst.[19b,c] The initial studies showed that the desired amide **3aa** formed in all the tested solvents, including acetonitrile (ACN) and dimethylformamide (DMF), which are routinely used in flavin oxidative catalysis, as well as in the less polar solvents, trifluoromethylbenzene (BTF), dichloromethane (DCM), ethyl acetate (EA), and tetrahydrofuran (THF) (Table 1, entries 1−6). The formation of byproducts arising from **RFTA** photocatalysis (see mechanistic studies below): carboxylic acid **4a**, formed by 4-chlorobenzaldehyde (**1a**) oxidation, and 1-formylpiperidine (**5a**) formed from piperidine (**2a**) were also observed. Therefore, the quantities of the byproducts became an important criterion for solvent selection. In addition, the practical aspects of developing a method suitable for preparative-scale synthesis were considered.[22]

Amidation reactions in DCM and DMF occurred avoiding carboxylic acid **4a** formation (Table 1, entries 2, 3). However, the use of these solvents was rejected because of difficulties in pilot plant preparative experiments: problems with removal of DMF traces from the reaction mixtures and the volatility of DCM at slightly elevated temperatures, which was shown to promote amide formation (Table 1, cf. entries 2, 5, 6 with 7−9).[23] Moreover, in DCM, an undesirable polymerization reaction was observed. Finally, ACN and THF, being the most suitable solvents not promoting formation of the byproduct, 1-formylpiperidine (**5a**) were selected. Moreover, oxidation to carboxylic acid **4a** can be suppressed by the addition of more amine (Table 1, entries 10−15), although an

Table 1. Optimizing Conditions for Amidations[a,b]



			yield [%][c]			
entry	solvent	conditions alternation	**1a**	**3aa**	**4a**	**5a**
1	BTF		18	65	17	21
2	DCM	40 °C	27	73	0	10
3	DMF		13	87	0	17
4	EA		15	60	25	4
5	ACN		7	63	30	0
6	THF		12	60	28	0
7	DCM	25 °C, 48 h	38	62	0	20
8	ACN	25 °C	51	43	6	5
9	THF	25 °C	51	49	0	8
10	ACN	1.2 equiv of **2a**	31	51	18	0
11	ACN	3 equiv of **2a**	2	80	18	0
12	ACN	4 equiv of **2a**	9	91	0	45
13	THF	1.2 equiv of **2a**	23	25	37	15
14	THF	3 equiv of **2a**	13	87	0	0
15	THF	4 equiv of **2a**	0	100	0	38
16	ACN	no MS	13	51	36	0
17	ACN	no RFTA	29[d]	0	0	0
18	ACN	no light	39[d]	0	0	0

[a]Selected data; for further experiments, see Supporting Information S4. [b]Conditions: **1a** (0.14 mmol), **2a** (0.28 mmol), **RFTA** (5 mol %), MS 3 Å (15 mg), solvent (250 μL), 448 nm, 45 °C, oxygen (balloon), 24 h. [c]Determined by ^{1}H NMR; yield of **5a** is related to amount of **2a**. [d]Adduct **6** is formed from **1a**.

excess of amine should be adjusted to avoid **5a** formation (Table 1, entries 12, 15). Blank experiments confirmed the essential role of light and catalyst as well as the beneficial effect of molecular sieves in amidation (Table 1, entries 16−18).

In parallel, the mechanism of amidation and byproduct formation was investigated. First, an experiment with ^{13}C/deuterium-labeled benzaldehyde was performed (Scheme 1A). As expected, amide **3ba** and carboxylic acid **4b** contained exclusively ^{13}C in the carboxylic function (see mass spectrometry analysis in Supporting Information S6). However, 1-formylpiperidine (**5a**) did not contain a ^{13}C atom demonstrating that benzaldehyde was not the source of the formyl group. The role of the solvent in formylation can also be excluded as formation of 1-formylpiperidine (**5a**) was observed in all tested solvents, including THF and BTF. Most probably, **5a** was formed by the oxidative cleavage of the piperidine dimer (**I**) whose formation was possible under oxidative conditions from piperidine (Scheme 1B, see Supporting Information S7 for mechanistic details).[24] Indeed, 1-formylpiperidine (**5a**) was formed when piperidine alone was irradiated in THF or ACN in the presence of **RFTA**. Analogous photocatalytic amine formylation has been described with Rose Bengal.[25] Regarding the other byproduct, benzoic acid **4a** was not formed by amide hydrolysis but by benzaldehyde oxidation as was proven by independent experiments (Scheme 1C, see Supporting Information S9). Electron transfer from benzaldehyde to excited **RFTA** is

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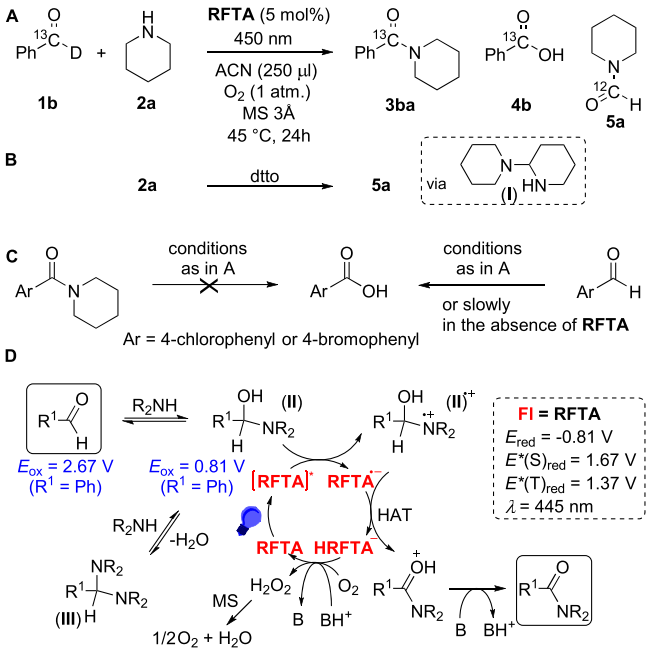
Scheme 1. Experiments with Isotope-Labelled Substrate (A), Other Control Experiments (B,C), the Proposed Mechanism of Oxidative Amidation with RFTA and the Corresponding Electrochemical (vs SCE) and Spectral Data in ACN (D)[a]

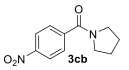
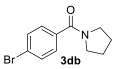
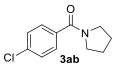
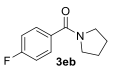
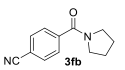
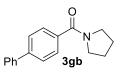
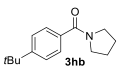
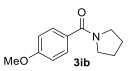
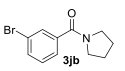
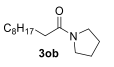
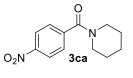
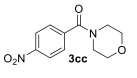
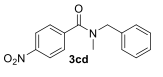


[a]The position of the unpaired electron in (**II**)$^{\bullet+}$ and the oxidation potentials were obtained by quantum chemical calculations (see Supporting Information S3, S10−S12).

thermodynamically disfavored; thus, one can expect oxidation by singlet oxygen,[26] which is known to be produced by **RFTA** sensitization.[27] Alternatively, autocatalytic oxidative process with triplet oxygen can be involved as slow oxidation of 4-chlorobenzaldehyde (**1a**) to acid **4a** was also observed in the absence of **RFTA**.[28]

The proposed mechanism for amidation (Scheme 1D) is based on the already known behavior of **RFTA** in photooxidations[21] and on our own experiments. In the presence of an amine, aldehyde reversibly forms the corresponding aminal (**II**) as monitored by ^{1}H NMR and HR-MS spectrometry (see Supporting Information S8). Interestingly, the diamino-species (**III**) can be slowly formed if the aminal (**II**) is not consumed, for example, in the absence of light or catalyst (Table 1, entries 17, 18). The aminal (**II**) has a substantially lower oxidation potential compared with the aldehyde (and even the amine, E_{ox} (**2a**) = 1.3 V[29] vs saturated calomel electrode (SCE)) which makes electron transfer (ET) to an excited **RFTA** feasible, regardless of whether it is in a singlet or triplet excited state (see Scheme 1D for the electrochemical data). Additionally, the possibility of ET between **RFTA*** and (**II**) was confirmed by efficient **RFTA** fluorescence quenching with 1-[methoxy(phenyl)methyl]piperidine (**II′**), an isolatable model of (**II**) (see Supporting Information S8). After ET, hydrogen atom transfer (HAT) occurs between (**II**)$^{\bullet+}$ and **RFTA**$^{\bullet-}$. Alternatively, proton transfer to form the aminal (**II**)$^{\bullet}$-**RFTA**$^{\bullet}$ radical pair followed by HAT can occur.[21a] Finally, the reduced flavin is reoxidized by oxygen from its reduced form under formation of hydrogen peroxide as the side product according to the analogy with other flavin-based photooxidations.[18a,e] Hydrogen peroxide is immediately decomposed by MS and thus cannot be involved in an oxidative process.[19c]

Table 2. Scope of Amidation with RFTA[a]

Entry	Substrate	Amine equiv.	Time [h]	Conv. [%]	Yield [%]
1[b]	 3cb	2	4	quant.	85
2	 3db	2	4	quant.	74
3	 3ab	2	4	quant.	62
4	 3eb	3	3	quant.	65
5	 3fb	2	2.5	quant.	98
6	 3bb	4	4	quant.	53
7	 3gb	2.5	3	91	51
8	 3hb	4	4	quant.	52
9	 3ib	5	3	quant.	50
10	 3jb	3	4	quant.	52
11	 3kb	3	4	96	58
12	 3lb	2	3.5	quant.	64
13	 3mb	2	4	quant.	65
14	 3nb	5	4	quant.	15
15	 3ob	4	4	quant.	10
16	 3pb	2.5	3.5	quant.	19
17	 3qb	4	4	quant.	30
18[b]	 3ca	2	4	quant.	88
19	 3cc	2	2.5	94	69
20	 3cd	4	5	quant.	68

[a]Conditions: substrate (1 mmol), **RFTA** (5 mol %), MS 3 Å (125−150 mg), THF (2 mL), 448 nm, ambient temp., oxygen (balloon); see Supporting Information S2 for details. [b]Acetonitrile instead of THF.

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On the basis of the findings from the analytical experiments and mechanistic studies, conditions for preparative experiments on a 1 mmol scale were devised and a substrate scope was investigated. THF was predominantly used as the solvent, nevertheless reactions could be performed in ACN with similar yields (see Supporting Information S5). Aldehydes containing an electron-donating group were observed to be less reactive than those containing an electron-withdrawing group, which was demonstrated by a decreased tendency of electron-rich aldehydes to form the adduct (**II**). Moreover, very electron -rich aldehydes like 4-methoxybenzaldehyde (**1i**) underwent ET photooxidation with **RFTA**.[21a] To eliminate this side oxidation and to support adduct formation, more amine equivalents were used for less-reactive amines. Under these optimized conditions, the desired aromatic amides **3** were obtained in good to high preparative yields after 2−5 h irradiation (Table 2). Interestingly, beside para-substituted benzaldehydes (Table 2, entries 1−9), the reaction can be performed with meta- and ortho-substituted benzaldehydes (Table 2, entries 10, 11) and heteroaromatic derivatives (Table 2, entries 12, 13). The method was found to be applicable to aliphatic aldehydes (Table 2, entries 14−17). The method was also demonstrated to be useful for other secondary amines (Table 2, entries 18−20) including benzylic and acyclic amines. Reactions with primary amines afforded only imines via aldehyde-amine condensation reaction (data not shown). In many cases, complete conversion of the aldehyde was observed according to TLC and ^{1}H NMR; however, preparative yields were lower. This was predominantly true for the amides of aliphatic aldehydes because of significant losses during workup and by their decomposition. Interestingly, formation of carboxylic acids **4** was not observed by ^{1}H NMR in the reaction mixtures after preparative experiments done under optimized conditions.

In summary, it has been shown that the photooxidative properties of flavins could be helpful in the oxidative coupling of aldehydes with secondary amines. On the basis of these properties, a novel and fast metal-free procedure was developed which used a readily available riboflavin (vitamin B2) derivative, oxygen as terminal oxidant and could be used effectively for a broad range of aldehydes (including aliphatic), thus distinguishing it from already known aerobic catalytic methodologies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02391.

Experimental part including general procedures, characterization of amides and quantum chemical calculations; preliminary experiments on amidations on analytical and preparative scale; details on mechanistic studies; experimental setup for amidations; hardcopy of NMR data for **3**; geometries and energies for calculated molecules (PDF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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