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Carbamoylation of Azomethine Imines via Visible-Light Photoredox Catalysis

Bianca T. Matsuo, Pedro H. R. Oliveira, José Tiago M. Correia, and Márcio W. Paixão*

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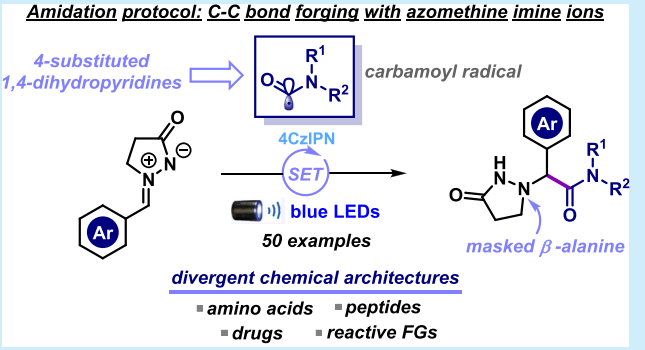
ABSTRACT: A versatile and robust photocatalytic methodology to install the amide functional group into azomethine imine ions is described. This protocol is distinguished by its broad scope and mild reaction conditions, which are well suited for the preparation of structurally complex compounds in the form of amino acids, peptides, and small drug-like molecules. Moreover, the generated pyrazolidinone core could be easily converted into β-alanine analogues.



Synthetic protocols for the preparation of amide-containing molecules are among the most valuable transformations in modern organic synthesis,[1] given the abundance of these motifs in biomolecules (as peptides and proteins), pharmaceuticals, and agrochemicals. Although significant advances have been made for the direct synthesis of amides, established routes are mainly based on C−N bond-forming reactions. Traditionally, these are performed by the condensation of carboxylic acids or derivatives with amines (Scheme 1a, left); however, C−C disconnection to install amide bonds offers new synthetic strategies to incorporate the amide motif that are complementary to the well-established routes. In this scenario, isocyanates and isocyanides have been explored in metal-catalyzed amidations[2] and in multicomponent approaches[3] (Scheme 1a, right).

Considered a contemporary challenge, significant effort has been focused on the development of new synthetic routes to selectively forge amide bonds, especially in complex molecules. The ability to leverage these methodologies for applications in antibody−drug conjugates within the context of biopharmaceutical discovery programs is needed and is essential for their success.[4]

Recently, photoredox catalysis have emerged as a valuable synthetic tool for the synthesis and modification of biomolecules and complex structures.[5] Among the photocatalytic amidation approaches reported,[6] direct C−C bond formation strategies rely on the use of photocatalytic generated carbamoyl radicals as amide synthons. Recent literature has shown the use of oxamic acids[7] and *N*-oxyphthalimido oxamides[8] in oxidative and reductive decarboxylative approaches, respectively (Scheme 1b, left).

Last year, the groups of Melchiorre[9] and Jacobi von Wangelin[10] explored dihydropyridine (DHP) derivatives as an alternative strategy to install amide bonds on (hetero)aryl bromides and activated olefins, respectively. By the exploration of electron donor−acceptor (EDA) complexes with DHPs, Hong[11] disclosed a cross-coupling reaction using *N*-amidopyridinium compounds, including in the scope examples of C4-carbamoylated pyridines (Scheme 1b, right). The reactive radical species generated through these protocols contain the amide functionality ready to be installed, and in comparison with metal-catalyzed approaches, it could be considered a nucleophilic reduced equivalent of isocyanates (Scheme 1c).

Inspired by these initial findings, we rationalized that an unprecedented photocatalytic carbamoylation of imines would represent a mild and easy strategy for constructing biologically relevant scaffolds and would complement those protocols involving the functionalization of aryl halides,[9] activated olefins,[10] and aza-heterocycles.[7b,11,12]

The selected coupling partners, azomethine imine ions, are known as important building blocks that can be easily transformed into biologically relevant nitrogen-containing heterocycles.[13] This class of molecules has been exhaustively explored as 1,3-dipoles; however, only recently has their reactivity toward photocatalytic radical addition been inves-

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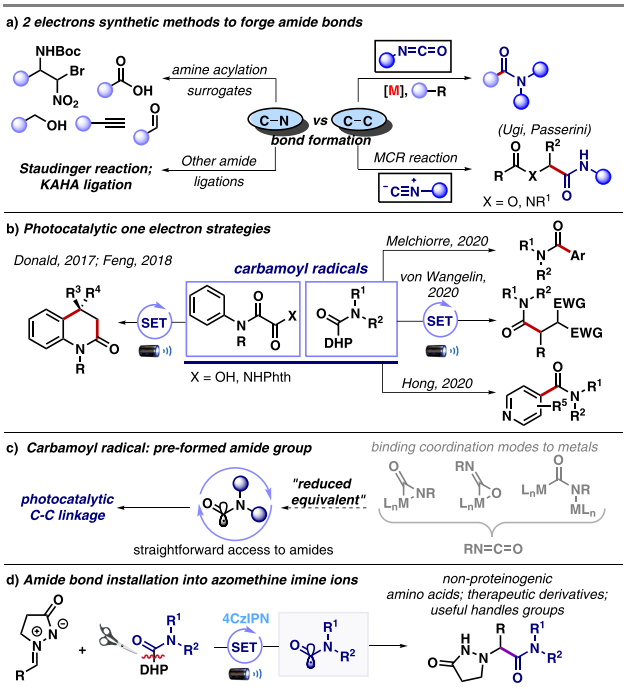
Scheme 1. (a) C−C and C−N Strategies for Amide Ligation Construction, (b) Recent Photocatalytic One-Electron Generation of Carbamoyl Radicals, (c) Comparison of Preformed Amide Group in Carbamoyl Radical and Isocyanate-based Methodologies, and (d) Our Proposal: Installation of Secondary/Tertiary Amides into Azomethine Imines



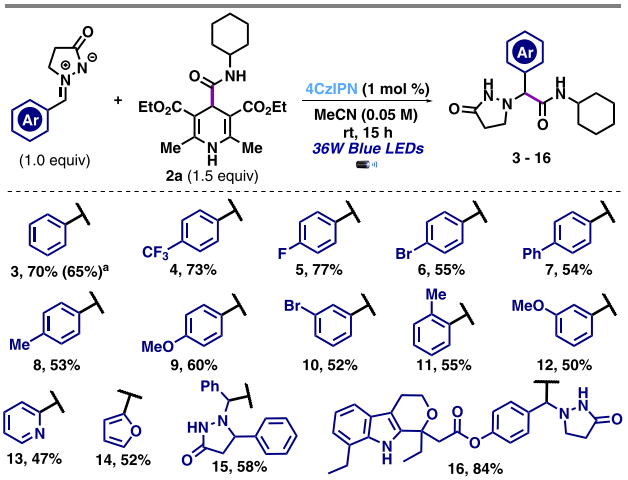
tigated.[14] In this work, we describe the construction of valuable amide compounds in a C−C bond-forging strategy between DHP derivatives and azomethine iminium ions in a mild and robust protocol (Scheme 1d).

Four-substituted 1,4-dihydropyridines (DHPs) are bench-stable solids. They are easily synthesized from commercially available starting materials and offer high structural diversification.[15] In addition to the exploration of DHPs as alkyl, acyl, and proton sources, they are also useful precursors for the generation of the less explored carbamoyl radicals under photocatalytic conditions. Because of their facile photoredox-catalyzed oxidation ($E_{ox} \approx +1.05$ V vs SCE), they are prone to undergo single-electron oxidation under visible-light irradiation in the presence of a suitable photocatalyst to provide the corresponding radical after fragmentation. Considering the advantages of the metal-free organic photocatalysts, we envisioned 4CzIPN to be a suitable catalyst to promote the proposed carbamoylation reaction ($E_{1/2}(PC^*/PC^-) = +1.35$ V vs SCE).[16]

Our study began using the azomethine iminium ion **1a** and the cyclohexylamine-derived dihydropyridine **2a** ($E_{ox} = +1.21$ V vs SCE; see cyclic voltammetry in the Supporting Information (SI)) as model substrates for the evaluation of the effect of various parameters on the reaction outcome. We identified that using only 1 mol % of the photocatalyst, we were able to obtain the corresponding product *N*-cyclohexyl-2-(3-oxopyrazolidin-1-yl)-2-phenylacetamide **3** in 70% yield in acetonitrile under 456 nm blue light-emitting diode (LED) irradiation. (See the SI for the complete optimization.)

Having established the optimal reaction conditions, we began to evaluate the scope of this transformation for a range of aryl azomethine imine ions (Scheme 2). As seen in Scheme 2, aryl azomethine imines bearing either electron-withdrawing

Scheme 2. Scope of Azomethine Imines[b]



[a]1.0 mmol scale. [b]Reactions were performed using azomethine imine (0.15 mmol), carbamoyl radical precursor (1.5 equiv, 0.225 mmol), and 4CzIPN (1 mol %) in MeCN (3.0 mL). The yields refer to isolated compounds after purification.

substituents (*p*-CF_3 **4** or *p*-F **5**) or electron-donating groups (*p*-Me **8** or *p*-OMe **9**) underwent carbamoylation with **2a** in moderate to good yield. Importantly, substrates containing aryl bromides could be successfully tolerated, allowing for further functionalization by transition-metal-mediated cross-coupling reactions (compounds **6** and **10**). Other substitution patterns did not show a substantial influence on the reaction outcome and, notably, ortho and meta substitutions were well tolerated (**11**, **10**, and **12**, respectively). Likewise, pyridine (**13**) and furan (**14**), privileged pharmacophores, were also competent toward the carbamoyl radical installation. The azomethine imine bearing a phenyl substituent on the pyrazolidinone ring was also compatible with the reaction conditions, furnishing the product **15**.

To demonstrate this method's applicability in the late-stage functionalization of dense molecules, we prepared a substrate derived from etodolac, an anti-inflammatory and analgesic drug. This structure possesses benzylic C−H bonds and acidic N−H bonds, which are known to interfere with radical pathways. Gratifyingly, subjecting this substrate to our reaction conditions, we were able to access the desired product **16** in excellent yield.

Recently, the use of nitrones in photoredox protocols has been reported in (3 + 2) cycloadditions[17] and in radical addition reactions.[18] Considering the importance of this structure to easily access nitrogen-containing compounds and the presence of *N*-hydroxylamines in pharmaceuticals,[19] we were curious if nitrone derivatives could be amenable to our optimized reaction conditions. To our delight, the carbamoylation proceeded well for all cases, affording the respective phenylglycine amide derivatives **17**−**19** in good yields (Scheme 3).

The growing application of modified peptides as drug candidates lead us to evaluate the feasibility of the developed visible-light-mediated protocol in the direct installation of proteinogenic amino acids across the azomethine imine

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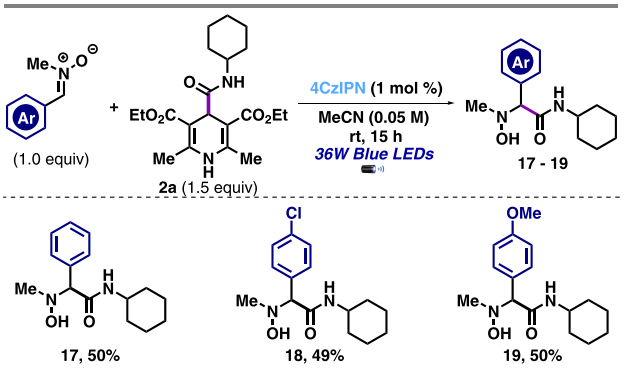
Scheme 3. Scope of Nitrones[a]



[a]Reactions using nitrone (0.15 mmol), carbamoyl radical precursor (1.5 equiv, 0.225 mmol), and 4CzIPN (1 mol %) in MeCN (3.0 mL). The yields refer to isolated compounds after purification.

scaffold. Such a combination allows the synthesis of non-natural amino acids and the assembly of modified peptides in a single event (Scheme 4, top, left).

Gratifyingly, the reaction tolerated a broad scope of amino acid derivatives, including those containing a nonpolar side chain (L-Val, L-Ala, L-Pro, L-Met and L-Ile), polar uncharged (L-Ser) and aromatic systems (L-Tyr, L-Trp and L-Phe), which could be smoothly transformed in good chemical yields (compounds **20**−**30**). Nonproteinogenic amino acids from L-(+)-α-phenylglycine and 2-methylalanine were nicely incorporated into the azomethine imine, providing compounds **31** and **32**, respectively.

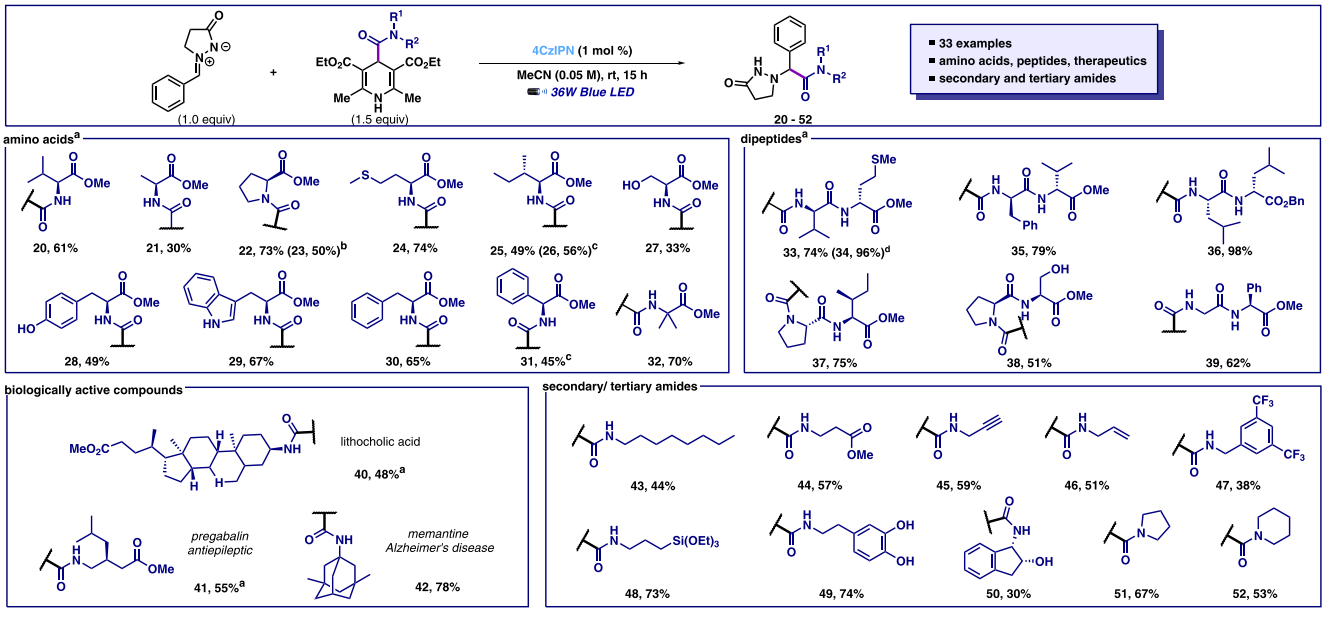
To further demonstrate the versatility of our method, we next turned our attention to explore the reactivity of dipeptides with the azomethine imine **1a** (Scheme 4, top, right). Pleasantly, the protocol allowed the synthesis of tripeptides containing a modified phenylglycine residue in good to high yield (compounds **33**−**39**), showcasing possible opportunities for the exploration of bioconjugation strategies. The dipeptide scope included sequences having L-Val, L-Met, L-Phe, L-Leu, L-Pro, L-Ser, L-Ile, and L-Phg residues, which contain useful handle groups for further modification of the peptide side chain. Notably, oxidation-labile methionine residues were well tolerated under our protocol.

As a further demonstration of the utility of the radical addition protocol, we examined the ability to generate hybrid architectures containing natural products and medicinal agents (Scheme 4, bottom, left). As shown, the pendant steroid lithocholic acid exhibited good reactivity with **1a**, giving rise to the highly functionalized adduct **40** in moderate chemical yield. Moreover, drug-like small molecules from the anti-epileptic pregabalin and memantine, used in the treatment of the Alzheimer's disease, were successfully installed into **1a** in good to excellent yield (compounds **41** and **42**, respectively).

Our method is also amenable to amides derived from other primary and secondary amines with unmasked functional handles groups (Scheme 4, bottom, right). Likewise, aromatic and aliphatic carbamoyl radicals were successfully installed as the electron-poor 3,5-CF_3-aromatic carbamoyl radical (**47**). Unprotected functional groups including alkyne (**45**), alkene (**46**), triethyl silicate (**48**), and phenol (**49**) did not dramatically affect the reaction outcome, affording the respective carmoylated products in moderate to good yields.

To showcase the utility and importance of our carbamoylated products, we next subjected examples of the obtained analogues to structural modification (Scheme 5). The pyrazolidinone moiety of the obtained structures can be considered a masked form of the nonproteinogenic amino acid β-alanine. Notably, the primary amide group is a key structural motif as a useful building block and is also present in many pharmaceutical compounds. The carbamoylated product **3**

Scheme 4. Scope of 4-Carbamoyl-1,4-Dihydropyridines[e]



[a]Compounds obtained as a mixture of 1:1 dr. [b]Using the 3-phenyl substituted pyrazolidinone azomethine imine. [c]Using the p-$CF_3C_6H_4$ azomethine imine. [d]Using the p-BrC_6H_4 azomethine imine. [e]Reactions using azomethine imine (0.15 mmol), carbamoyl radical precursor (1.5 equiv, 0.225 mmol), and 4CzIPN (1 mol %) in MeCN (3.0 mL). The yields refer to isolated compounds after purification.

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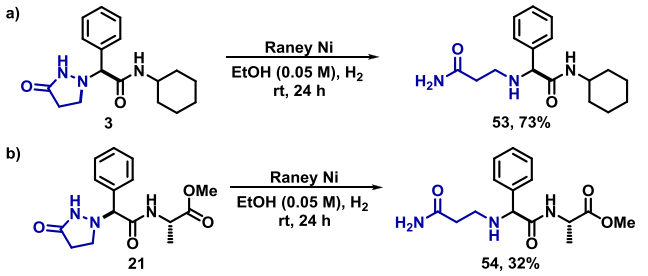
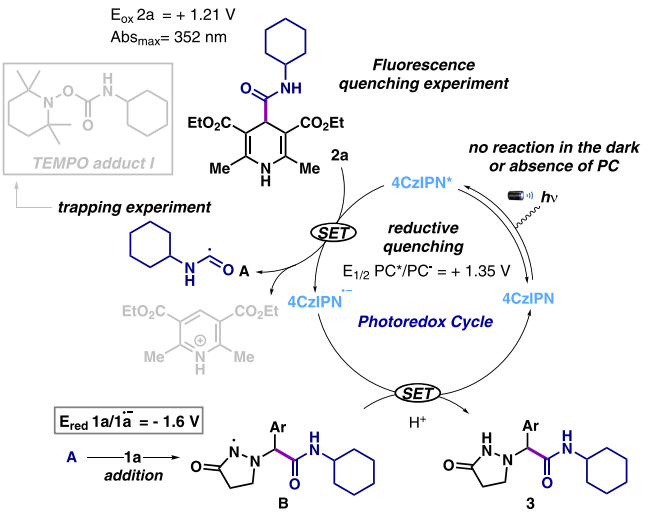
Scheme 5. Reductive Cleavage of the Pyrazolidinone Moiety



could be selectively reduced using pretreated Raney Ni under a H_2 atmosphere at room temperature, delivering the amino propanamide **53** (Scheme 5a). The product containing the L-Ala residue **21** was sequentially submitted to the same reductive conditions, affording the primary amide **54** (Scheme 5b).

On the basis of control experiments and the previous reports, we propose a plausible mechanism for the carbamoylation reaction in Scheme 6 (See the SI for details).

Scheme 6. Proposed Mechanism for the Carbamoylation of Azomethine Imines



Under 456 nm blue LED irradiation, the photocatalyst 4CzIPN (λ = 507 nm) is efficiently converted to its long-lived triplet excited state 4CzIPN* (τ = 5.1 μs).[20] The 4CzIPN* ($E_{1/2}(PC^*/PC^-)$ = +1.35 V vs SCE)[16] is oxidizing enough to promote the SET oxidation of **2a** (E_{ox} **2a** = +1.21 V vs SCE), which after fragmentation, generates the corresponding carbamoyl radical **A**. The addition of **A** to the azomethine iminium **1a** gives rise to the amidyl intermediate **B** after a spin-center shift event. Furthermore, this reactive intermediate undergoes SET reduction with the reduced photocatalyst to provide, after protonation, the desired product. It is important to emphasize that the SET reduction of **1a** should not be feasible given its highly negative reduction potential (E_{red} **1a** = −1.6 V vs SCE and $E_{1/2}(PC^+/PC^*)$ = −1.04 V vs SCE).

Moreover, the fluorescence quenching study within the redox potentials corroborates the identification of the reductive quenching of the photocatalyst as the initial mechanistic step.

Additionally, the reaction in the presence of the radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, 3 equiv) did not lead to the formation of the product, and the TEMPO adduct **I** was detected. Control experiments also disclosed the role of the irradiation source and the photocatalyst for the carbamoylation reaction outcome.

In summary, we demonstrate a robust photocatalytic strategy for the amidation of azomethine imines ions via C−C bond coupling reaction with readily available DHPs. This transformation allowed straightforward access to a wide range of carbamoylated compounds through a simple and versatile protocol using only 1 mol % of photocatalyst and a small excess of the radical precursor.

Crucially, the radical addition platform displayed high functional tolerance and amenability toward biologically relevant scaffolds as amino acids, peptides, drugs and compounds containing fragile functionalities as tertiary bonds and reactive groups. Therefore, the protocol represents a new strategy for the structural diversification of the chemical space of these important classes of compounds. Additionally, the direct application for obtaining primary amides from the simple reductive cleavage of the pyrazolidinone nucleus was demonstrated, leading to β-alanine derivatives containing multiple reactive sites liable to orthogonal derivatizations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02353.

Details of all experimental, electrochemical, and spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Márcio W. Paixão − *Centre of Excellence for Research in Sustainable Chemistry (CERSusChem), Department of Chemistry, Federal University of São Carlos − UFSCar, São Carlos, São Paulo 13565-905, Brazil;* orcid.org/0000-0002-0421-2831; Email: mwpaixao@ufscar.br

Authors

Bianca T. Matsuo − *Centre of Excellence for Research in Sustainable Chemistry (CERSusChem), Department of Chemistry, Federal University of São Carlos − UFSCar, São Carlos, São Paulo 13565-905, Brazil*

Pedro H. R. Oliveira − *Centre of Excellence for Research in Sustainable Chemistry (CERSusChem), Department of Chemistry, Federal University of São Carlos − UFSCar, São Carlos, São Paulo 13565-905, Brazil*

José Tiago M. Correia − *Centre of Excellence for Research in Sustainable Chemistry (CERSusChem), Department of Chemistry, Federal University of São Carlos − UFSCar, São Carlos, São Paulo 13565-905, Brazil*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c02353

Author Contributions

B.T.M. performed most of the experiments in this study and wrote the original version of this manuscript and the Supporting Information. P.H.R.O. performed the experiments for the scope evaluations and contributed to the Supporting Information preparation. J.T.M.C. prepared starting materials and, with M.W.P., reviewed, corrected, and provided useful

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contributions to the manuscript. All authors provided input on the manuscript.

Notes

The authors declare no competing financial interest.

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