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Visible-Light-Mediated α-Amino Alkylation of Azomethine Imines: An Approach to *N*-(β-Aminoalkyl)pyrazolidinones

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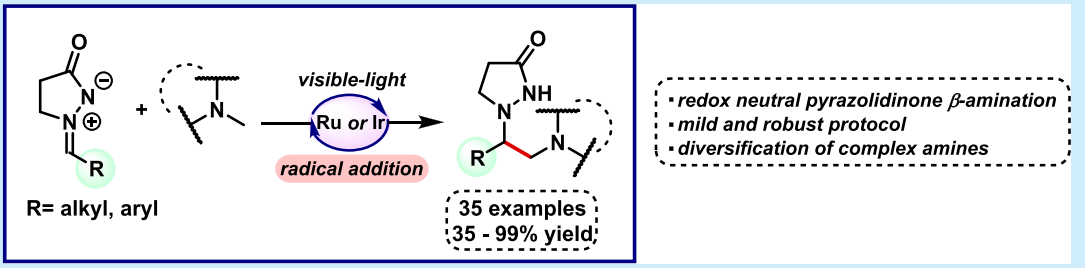

ABSTRACT: Herein, a mild and robust photocatalytic protocol for the combination of amino and pyrazolidinone functionalities through a radical α-amino alkylation of azomethine iminium ions is demonstrated. This method presents a high functional group tolerance providing direct access to a large family of *N*-(β-aminoalkyl)pyrazolidinones in good to excellent yields, including the late-stage incorporation of the pyrazolidinone moiety to pharmaceutical ingredients. We propose a plausible scenario for the C−C bond-forming step which involves radical addition followed by a spin-center-shift event.

Iminium ions play a significant role in synthetic organic chemistry, participating as strong electrophilic entities or intermediates in an array of two-electron processes. As electrophiles, they provide direct access to nitrogen-containing architectures frequently found in biologically active systems and are therefore particularly attractive to the pharmaceutical industry.[1]

Moreover, one-electron C−C bond-forming processes, notably, the coupling of alkyl radicals to iminium ions,[2] have substantially been reported in the literature and are envisaged as a suitable alternative to the addition of alkyl-Grignard reagents.[3] These radical-based reactions normally occur in the presence of stoichiometric amounts of SET (single electron transfer) reductants like alkylstananes,[4,5] benzylsilanes,[5] Ti(III) (Porta reaction), or trialkylboranes with the iminium ion preformed or in situ generated from the respective amine, imine, or imine derivative (e.g., oximes and hydrazones) (Scheme 1A).

Nitrogen-centered 1,3-dipoles are versatile building blocks for the preparation of five-membered heterocyclic systems. Despite recent advances in photocatalyzed [3 + 2] cycloadditions, the use of nitrogen-centered 1,3-dipoles, other than nitrones and azides, in different classes of photocatalyzed reactions remains underexplored.[6] In this context, azomethine imines (3-oxopyrazolidin-1-ium-2-ides) are broadly known as important building blocks for the preparation of synthetically and biologically relevant dinitrogen-fused heterocycles (Scheme 1B). These molecules present a zwitterionic nature which has been mainly explored in 1,3-dipolar cycloadditions. Such methodologies are considered powerful protocols for preparation of five- and six-membered dinitrogen-fused heterocycles simply through the combination of the dipole system with unsaturated nitriles,[7] vinylogous azaenamines,[8] pyrazolidinium ylides,[9] aldehydes[10] and α,β-unsaturated aldehydes,[11] α-acidic isocyanides,[12] allenoates,[13] Morita−Baylis−Hillman carbonates,[14] azlactones,[15] and *p*-quinols,[16] among others (Scheme 1C).

On the other hand, limited examples of UV-promoted photoisomerization and photocyclization of azomethine iminium ions can be found in the literature.[17] Nevertheless, only recently has reactivity of these unique substrates under visible-light photoredox catalytic conditions been demonstrated by Yang and co-workers. In their work, a radical−radical coupling between α-aminomethyl radicals originating from the photoreduction of azomethine imines and difluoroalkyl radicals gave rise to a comprehensive family of difluorinated 3-pyrazolidinones (Scheme 1D).[18]

The amino group is a common structural featured in many natural products and pharmaceuticals, and consequently, the visible-light-mediated photocatalytic generation of α-amino radicals from tertiary amines and their application to a diverse

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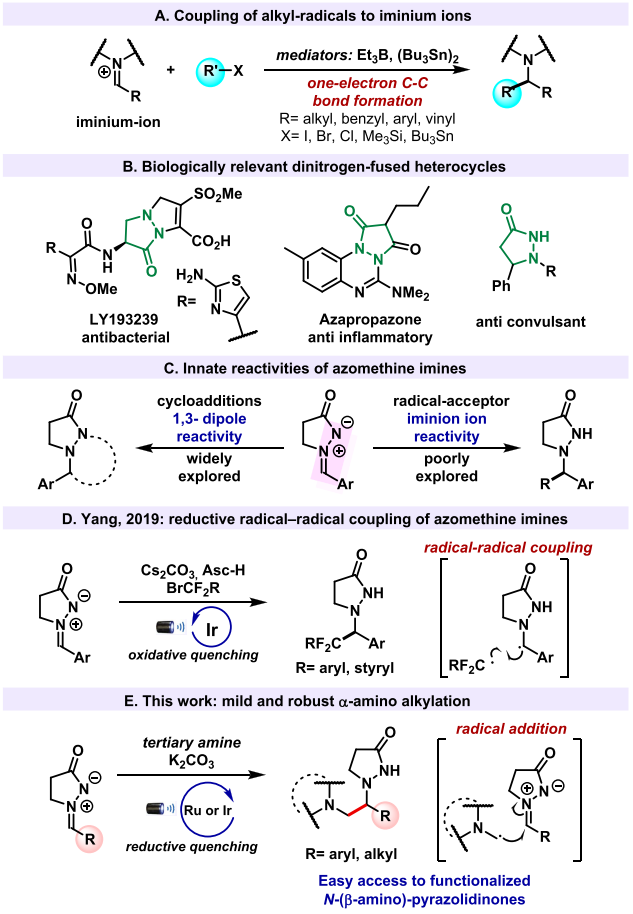
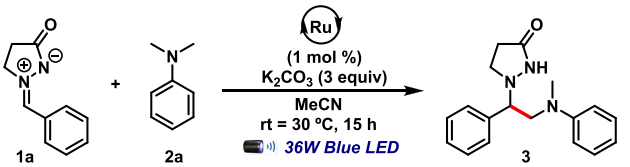
Scheme 1. (A) Classical Approaches for Radical Addition to Iminium Ions. (B) Relevant Compounds Containing Pyrazolidinone Ring. (C) Explored Reactivities of Azomethine Imines. (D) Recent Photocatalytic Protocol. (E) This Work



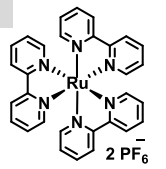
array of powerful synthetic transformations is a well-established approach.[19] Inspired by previous reports and the scarce development of visible-light-mediated transformations of azomethine imines, we envisioned that α-aminoalkyl radicals would be suitable coupling partners for the development of a new photoredox azomethine imine functionalization strategy, in which they would behave as iminium-ions instead of as the well explored 1,3-dipoles. The *N*-centered radical generated after the radical addition is prone to undergo a spin-center-shift event,[20] leading to a more stabilized amidyl radical which supports the feasibility of this proposal. This approach could yield densely functionalized *N*-(β-aminoalkyl)pyrazolidinones under mild reaction conditions (Scheme 1E).

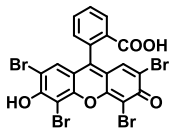
To evaluate the feasibility of this radical addition protocol, we started by studying the coupling of *N*,*N*-dimethylaniline **2a** (E_{ox}= 0.80 V vs SCE at 20 °C in MeCN)[21] with azomethine imine **1a** (E_{red}= −1.66 V vs SCE at 20 °C in MeCN, see SI) in acetonitrile, using K_2CO_3 as base and the ruthenium-based photocatalyst $[Ru(bpy)_3](PF_6)_2$ (**Ru**) ($E_{1/2}(M^{(II)*}/M^{(I)})$ = +0.77 V vs SCE in MeCN)[22] under blue LED irradiation (34 W Kessil H150 lamp λ= 456 nm) at room temperature (Table 1, entry 1). To our delight, under these conditions the desired product **3a** was obtained with excellent chemical yield. Likewise, iridium photocatalysts (**Ir-I**, **II**, and **III**) were also

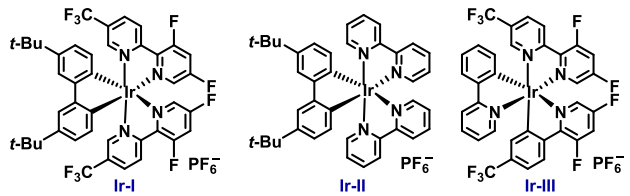
Table 1. Optimization of Reaction Conditions[a]



entry	deviation from standard conditions	3a (%)[b]
1	**none**	99
2	**Ir-I** instead of Ru	99
3	**Ir-II** instead of Ru	95
4	**Ir-III** instead of Ru	99
5	Ir-I and **no base**	traces
6[c]	**Eosin Y** instead of Ru	traces
7	**0.5 mol%** of Ru	84
8	reactional time of **7 h**	98
9	no photocatalyst	nr
10	without LED	nr
11	without degassing	37
12	in the presence of **TEMPO**	-







[a]Reaction conditions: **1a** (0.15 mmol), **2a** (2 equiv, 0.30 mmol), photocatalyst (1 mol %), and K_2CO_3 (3 equiv, 0.45 mmol) in MeCN (1.0 mL). [b]Isolated yield. [c]Under green-LED irradiation.

tested and successfully furnished **3a** in excellent yields (Table 1, entries 2−4).

When the reaction was conducted in the absence of base, only traces of **3a** were observed, showing that its presence is crucial for the generation of the desired initial radical intermediate (Table 1, entry 5). Additionally, eosin Y ($E_{1/2}(M^*/M^-)$ = +0.78 V vs SCE in MeCN), which exhibits similar electrochemical characteristics as Ru(II) photocatalyst,[23] was evaluated under similar reaction conditions. However, this organic photocatalyst was not efficient in promoting the transformation (Table 1, entry 6).

Unfortunately, decreasing the photocatalyst loading to 0.5 mol % led to an erosion in the chemical yield of **3a** (Table 1, entry 7). Moreover, the reaction time could be reduced to 7 h without affecting the yield (Table 1, entry 8). Ultimately, control experiments were carried out and demonstrated that the cooperative role between the photocatalyst, visible-light irradiation source, and the degassed conditions was essential for the effectiveness of the reaction outcome (Table 1, entries 9−11, respectively). Additionally, no product was observed when the reaction was carried out in the presence of the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidyl-1-oxyl), and 60% of the azomethine imine **1a** was recovered, thus confirming that a radical process is taking place (Table 1, entry 12).

With the optimized conditions in hand, the scope and limitations of this protocol were initially investigated in terms of a range of azomethine imines (Scheme 2). The methodology showed outstanding functional group tolerance, with the outcome of the process being almost unaffected by variations

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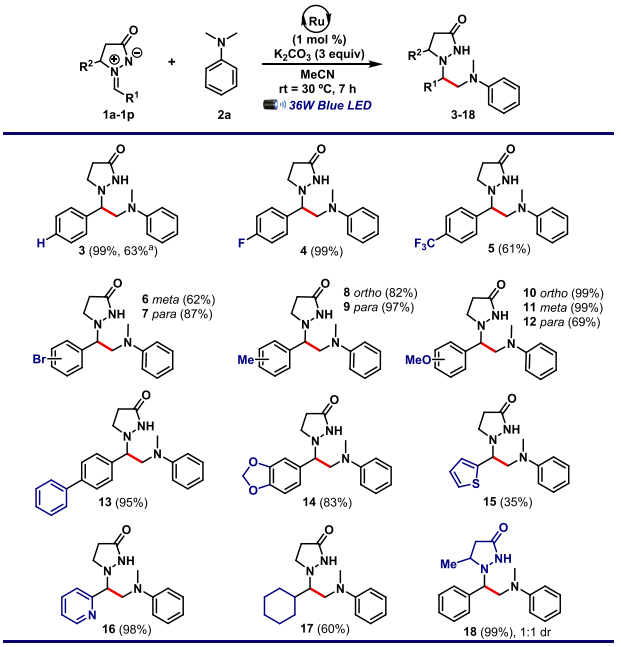
Scheme 2. Azomethine Imine Scope for the Functionalization Reaction with *N,N*-Dimethylaniline 2a*

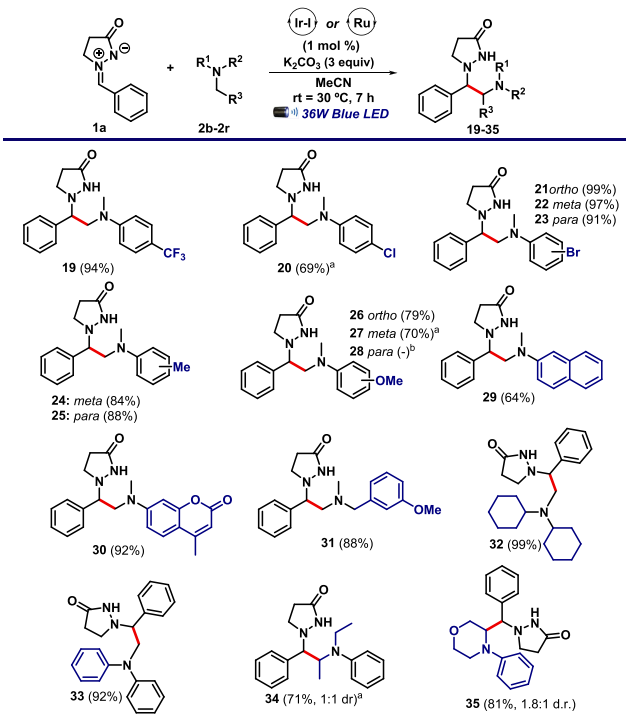


*Reaction conditions: **1a** (0.15 mmol), **2a** (2 equiv, 0.30 mmol), Ru (1 mol %), and K_2CO_3 (3 equiv, 0.45 mmol) in MeCN (1.0 mL). Yields refer to isolated compounds after column chromatography. [a]Yield for the reaction using 1 mmol scale.

in the aryl ring electron density and substitution patterns. Fluorinated substrates underwent the α-amino alkylation in moderate to excellent yields as observed for compounds **4** (99%) and **5** (61%). Bromine-substituted aryl substrates, which are important synthons in transition-metal-mediated cross-coupling reactions, also underwent the desired transformation smoothly, affording the corresponding products **6** and **7** in good yields (62% and 87%, respectively). The developed protocol also performed well when *ortho*-substituted azomethine imines were subjected to the optimized reaction conditions (**8** and **10**). Notably, substrates containing electron-donating groups displayed a similar chemical behavior, delivering the desired products in high chemical yields. Azomethine imines derived from thiophene-2-carbaldehyde afforded the corresponding product in low yield (**15**, 35%), while the azomethine imine derived from pyridine-2-carbaldehyde gave the α-amino alkylated product **16** in 98% yield. Interestingly, the cyclo aliphatic azomethine imine, which exhibits a lower reduction potential, underwent the functionalization in satisfactory yield (**17**). We further evaluated the azomethine imine derived from racemic 3-methylpyrazolidinone, envisioning possible applications on asymmetric synthesis of dinitrogen-fused heterocycles. Under the optimized conditions, this reaction was highly efficient, yielding product **18** in 99% yield as a 1:1 mixture of diastereoisomers. To further evaluate the scalability of the protocol, a 1 mmol scale experiment was performed, in which compound **3** was obtained in 63% yield (Scheme 2).

Next, we examined the scope and limitations with respect to the tertiary amine component. This study showed that the substituent nature on the aryl ring of the *N,N*-dimethylanilines displayed a crucial influence on the reaction outcome. Following these observations and aiming to expand the applicability of the current transformation, the use of a more oxidizing photocatalyst showed to be necessary. Therefore, replacing $Ru(bpy)_3(PF_6)_2$ by $Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (**Ir-I**) ($E_{1/2}(M^{(III)*}/M^{(II)})$ = +1.21 V vs SCE in MeCN)[22] allowed access to a range of *N*-(β-aminoalkyl)-pyrazolonidinones (Scheme 3).

Scheme 3. Tertiary Amine Scope for the Radical Coupling with 1a*



*Reaction conditions: **1a** (0.15 mmol), **2a** (2 equiv, 0.30 mmol), photocatalyst (1 mol %), and K_2CO_3 (3 equiv, 0.45 mmol) in MeCN (1.0 mL). Yields refer to isolated compounds after column chromatography. [a]Reactions conducted using Ru photocatalyst. [b]The starting material was recovered.

Regarding the diversification on the aromatic ring of the *N*-alkyl radical precursor, different substitution patterns and both electron-withdrawing and electron-donating groups performed well, providing the corresponding products (**19**−**25**) in satisfactory to excellent yields. Notably, chlorinated and brominated *N,N*-dimethylanilines were suitable under the reoptimized condition (**20**−**23**), opening up an orthogonal pathway for further derivatizations. Furthermore, an electron-donating group at the *para* position on the aryl system proved to be a limitation of this reaction protocol (**28**). Remarkably, other structurally diverse tertiary amines, including trialkyl and benzylic amines, as well as the pharmacologically relevant 7-(dimethylamino)-4-methylcoumarin, underwent this transformation with high selectivity and excellent yields (**29**−**34**). An *N*-aryl tertiary cyclic amine was also successfully challenged as an α-amino radical source in this transformation, providing the corresponding pyrazolidinone decorated with the morpholine framework with good yield (**35**). Unfortunately, benzyl tertiary amines such as *N*-phenyl 1,2,3,4-tetrahydroisoquinoline were not reactive under the established protocol.

The design of simple and mild strategies for modifying complex structures is a fundamental goal in pharmaceutical

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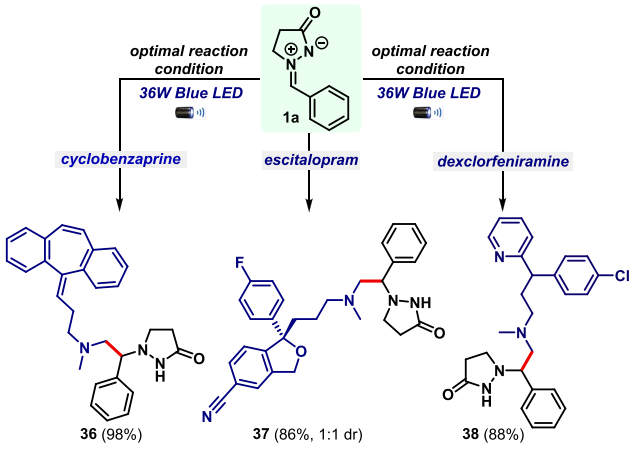
industries.[24] Driven by this observation, we sought to demonstrate a direct application of the developed protocol for the late-stage C−H modification of pharmaceutical ingredients. We found that azomethine imine **1a** could be smoothly incorporated onto the chemical architectures of the muscle relaxant cyclobenzaprine, the antidepressant escitalopram, and dexchlorpheniramine used as antihistamine in excellent yields (Scheme 4).

Scheme 4. Late-Stage Modification of Active Pharmaceutical Ingredients[a]



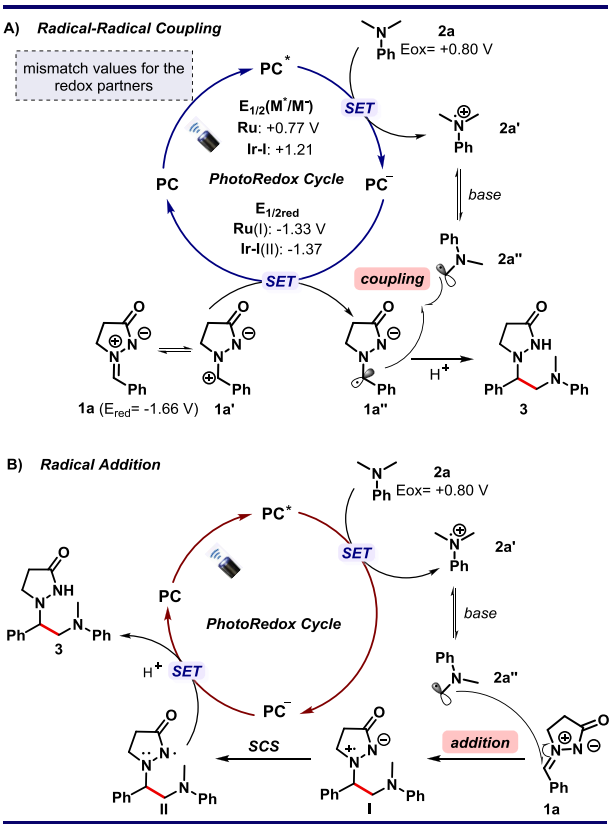
[a]Reaction conditions: **1a** (0.15 mmol), pharmaceutical compound (2 equiv, 0.30 mmol), **Ir-I** (1 mol %), and K_2CO_3 (3 equiv, 0.45 mmol) in MeCN (1.0 mL). Yields refer to isolated compounds after column chromatography.

Regarding the reaction mechanism, two pathways could be considered; they are strictly dependent on the relationship between the redox potential of the azomethine iminium ion and the photocatalysts employed. Both pathways begin with the quenching of the excited photocatalyst ($E_{1/2}$(M(II)*/M(I) = +0.77 V vs SCE in MeCN for Ru and $E_{1/2}$(M(III)*/M(II))= +1.21 V vs SCE in MeCN for **Ir-I**)[22] by the amine **2a**. In the presence of base, the radical cation **2a′** derived from this process is further converted to the respective transient α-amino alkyl radical intermediate **2a′′** (Scheme 5).

If the ground state of the reduced photocatalyst presents a suitable reduction potential, it would be able to reduce **1a** to the respective persistent α-amino alkyl radical **1a′′**.[25] A radical−radical coupling between these intermediates followed by protonation would afford the product **3** (Scheme 5A).[26] However, azomethine iminium ions has a high reduction potential (E_{red}= −1.66 V vs SCE at 20 °C in MeCN) and cannot be reduced by ground-state Ru(I) or Ir(II) (E_{red} = −1.33 V vs SCE at 20 °C in MeCN and E_{red} = −1.37 V vs SCE at 20 °C in MeCN, respectively) employed in this study.[22] Therefore, these facts rule out the possibility of a radical−radical coupling scenario.

On the other hand, taking into consideration the broad azomethine imine scope, we propose an alternative pathway in which the nucleophilic radical **2a′′** could directly attack **1a** to afford the *N*-centered cation radical intermediate **I** (Scheme 5B). Once formed, this intermediate is prone to undergo a spin-center-shift event (SCS) with the spin density located on the amide nitrogen. This event leads to an stabilized amidyl radical intermediate **II**, which would be reduced by the

Scheme 5. Proposed Mechanisms



ground-state Ru(I) or Ir(II) and protonated to provide the *N*-(β-aminoalkyl)pyrazolidinone **3**. This mechanistic scenario is more likely and is supported by previous reports in the literature.[26]

In conclusion, a new direct and efficient strategy for the installation of tertiary amines onto azomethine imines was developed. Under this new protocol, substrates with different electronic and steric features were nicely engaged in good to excellent yields and with high functional group tolerance. A very successful late-stage C−H modification of biologically relevant compounds was also demonstrated using the current developed methodology. We believe that this contribution will serve as a stimulus to the community in expanding the application of the azomethine iminium ions as radical acceptors under photocatalytic conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02821.

Experimental procedures, characterization data, and NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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