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VISIBLE-LIGHT-INDUCED FORMAL [3+2] CYCLOADDITION OF α,β-UNSATURATED IMIDES OR AMIDE WITH *N,N,N′,N′*-TETRAMETHYLDIAMINOMETHANE FOR THE SYNTHESIS OF 4-ALKYL- AND 4-ARYL-1-METHYL-2-PYRROLIDINONES

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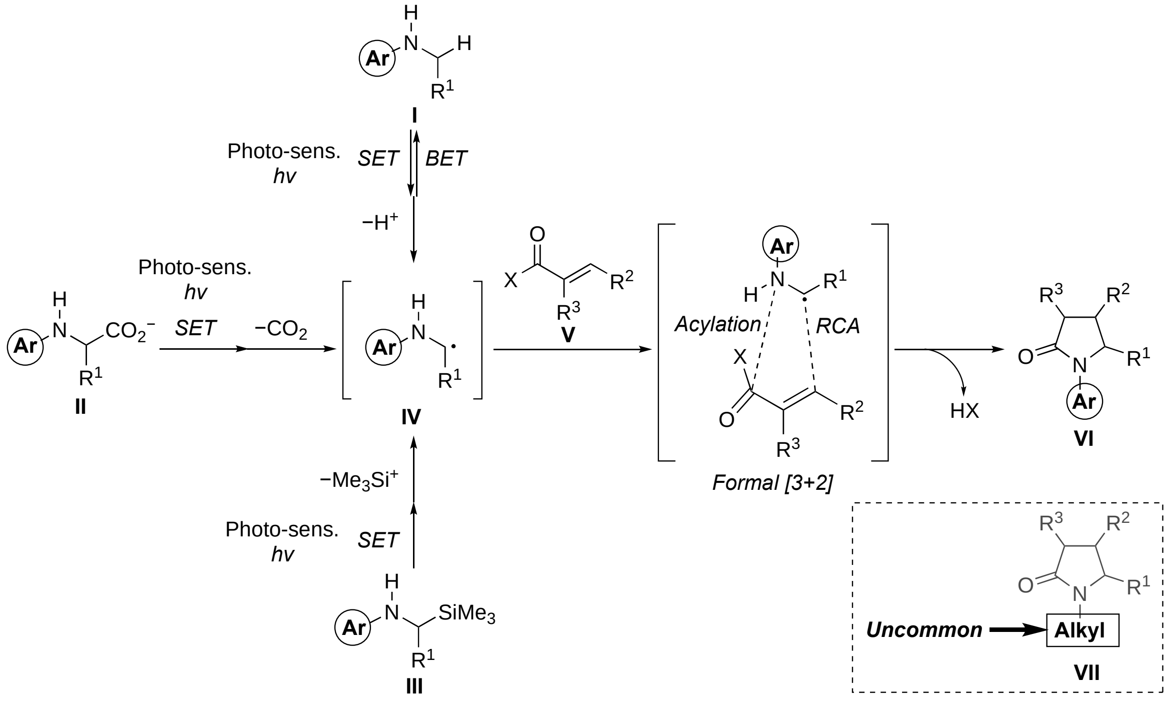
Abstract – We present herein a photochemical reaction to synthesize 4-alkyl- and 4-aryl-1-methyl-2-pyrrolidinones through the formal [3+2] photocycloaddition of α,β-unsaturated imides or amide with *N*,*N*,*N′*,*N′*-tetramethyldiaminomethane, where an iridium(III) complex acts as a photosensitizer. The reaction is driven by visible-light-induced single-electron transfer between a photoexcited iridium(III) complex and *N*,*N*,*N′*,*N′*-tetramethyldiaminomethane to generate an α-aminoalkyl radical. The resulting α-aminoalkyl radical is added to α,β-unsaturated imides or amide in a 1,4-fashion to produce conjugate adducts, subsequently causing intramolecular acylation to furnish 4-alkyl- and 4-aryl-1-methyl-2-pyrrolidinones.

INTRODUCTION

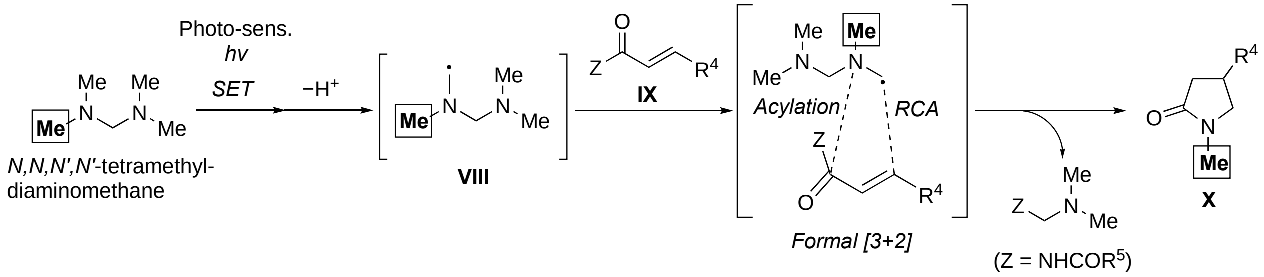
The formal [3+2] photocycloaddition of α,β-unsaturated compounds with α-aminoalkyl radicals is an attractive reaction because it enables the facile synthesis of many natural products and biologically active compounds containing a 2-pyrrolidinone skeleton.[1] The proposed reaction mechanism for the formal [3+2] photocycloaddition of α,β-unsaturated compounds with α-aminoalkyl radicals is described as follows (Scheme 1). *N*-Alkylarylamines **I**, *N*-arylglycines **II**, or *N*-[(trimethylsilyl)alkyl]arylamines **III** react with photoexcited photosensitizers through single-electron transfer (SET) processes, followed by deprotonation, decarboxylation, or desilylation to give the corresponding α-aminoalkyl radicals **IV**. However, the generation of an α-aminoalkyl radical **IV** from *N*-alkylarylamines **I** is still rare because the back electron transfer (BET) process competes with the SET, and hence, the subsequent deprotonation is slow.[1e,2] On the other hand, the generation of an α-aminoalkyl radical **IV** from *N*-arylglycines **II** or *N*-[(trimethylsilyl)alkyl]arylamines **III** is well established.[1a–1d,1f] The resulting α-aminoalkyl radical **IV** reacts with α,β-unsaturated compounds **V** through radical conjugate addition (RCA) followed by intramolecular acylation to give 2-pyrrolidinones **VI**. Although the reactions mentioned above enable the synthesis of highly substituted 2-pyrrolidones, aryl groups are typically placed on the nitrogen atom of the 2-pyrrolidinone ring. Therefore, achieving the allocation of alkyl groups to the nitrogen atom of the 2-pyrrolidinone ring of **VII** is still uncommon.[1a]



Scheme 1. Previously reported formal [3+2] photocycloaddition of α,β-unsaturated compounds with amines

In this report, we present the formal [3+2] photocycloaddition of α,β-unsaturated imides or amide to *N,N,N′,N′*-tetramethyldiaminomethane using an iridium(III) complex photosensitizer (Ir(III) complex), a reaction that enables the synthesis of 4-alkyl- and 4-aryl-2-pyrrolidinones possessing a methyl group on the nitrogen atom of the 2-pyrrolidinone ring (Scheme 2). Recently, we reported that *N,N,N′,N′*-

tetramethyldiaminomethane could be converted to the corresponding α-aminoalkyl radical **VIII** in a regioselective manner based on a stereoelectronic rule[3,4] under photosensitized conditions, in which α-aminoalkyl radical **VIII** reacts with nitrones or imines to give 1,2,5-oxadiazinanes or imidazolidines, respectively.[4] Therefore, we expected that α-aminoalkyl radical **VIII** would react with α,β-unsaturated imides, or amide **IX** in a formal [3+2] fashion to give 4-alkyl- and 4-aryl-1-methyl-2-pyrrolidinones **X**. We also demonstrated the synthesis of *N*-methylrolipram (4-(3-cyclopentyloxy-4-methoxyphenyl)-1-methyl-2-pyrrolidinone), a selective inhibitor of phosphodiesterase-4A4 (PDE4A4).[5]

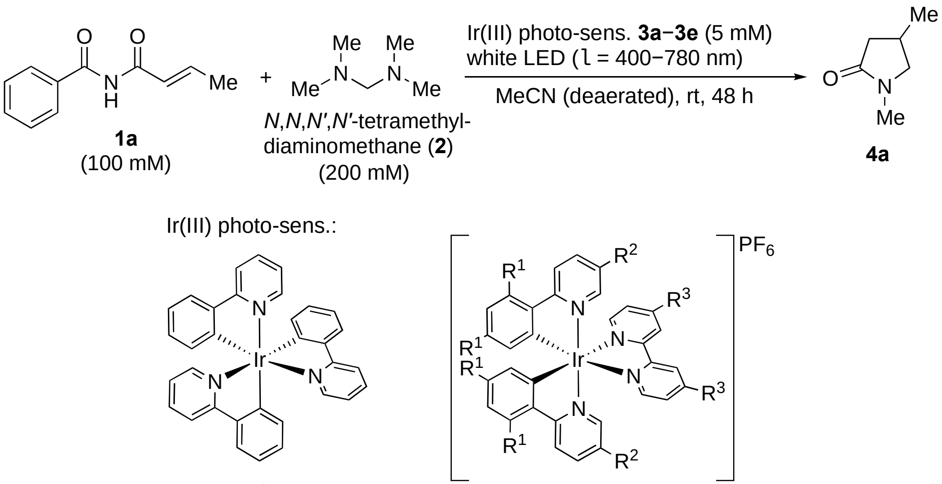


Scheme 2. Formal [3+2] photocycloaddition of α,β-unsaturated imides or amide with *N*,*N*,*N'*,*N'*-tetramethyldiaminomethanes (*Current study*)

RESULTS AND DISCUSSION

Formal [3+2] photocycloaddition of α,β-unsaturated imide **1a** with *N*,*N*,*N'*,*N'*-tetramethyldiaminomethane (**2**) was conducted in the presence or absence of several Ir(III) complexes **3a**–**3e** in MeCN under photoirradiation using a white LED light source (14 W) (Table 1). Yields of 1,4-dimethyl-2-pyrrolidinone (**4a**) were determined using quantitative NMR analyses. No reaction occurred in the absence of the Ir(III) complex, and imine **1a** was recovered (entry 1). In the initial investigation, tris(2-phenylpyridinato)iridium(III) (Ir(ppy)$_3$) (**3a**), which is prone to induce an oxidative quenching catalytic cycle,[6] was used as the photosensitizer. No reaction was observed under these conditions (entry 2). And then, we decided to use iridium(III) complexes which are generally used for amine oxidation to produce the α-aminoalkyl radical through a reductive quenching process.[6] Iridium(III) complex Ir(ppy)$_2$(5-CO$_2$Mebpy)PF$_6$ **3b** did not induce the reaction, leading to the recovery of imide **1a** (entry 3). The iridium(III) complexes Ir(ppy)$_2$(dtbpy)PF$_6$ **3c**, Ir(ppy)$_2$(dmobpy)PF$_6$ **3d**, and Ir[dF(CF$_3$)ppy]$_2$(dmobpy)PF$_6$ **3e** promoted the desired formal [3+2] photocycloaddition to give **4a** in yields ranging from 24 to 29%, which was not significantly different (entries 4–6). In our previous research, we revealed that **3e** is a more robust photosensitizer than **3c** and **3d**.[4] Therefore, we hypothesized that **3e** would still be a robust photosensitizer even if the reaction temperature was increased (Table 3). Finally, we designated photosensitizer **3e** as a standard photosensitizer to optimize the reaction conditions.

Table 1. Screening of photosensitizers



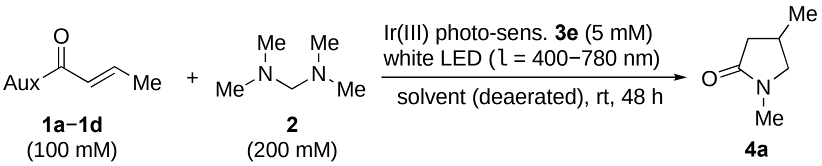
3b: R^1= R^2= R^3= H, R^3= CO_2Me
3c: R^1= R^2= R^3= H, R^3= *t*-Bu
3d: R^1= R^2= R^3= H, R^3= OMe
3e: R^1= F, R^2= CF_3, R^3= OMe

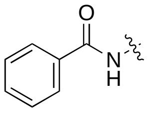
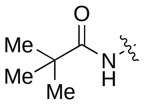
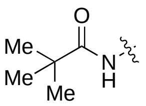
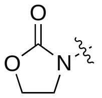
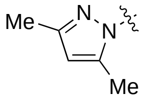
entry	photo-sens.	yield [%][a]
1	none	0
2	**3a**	0
3	**3b**	0
4	**3c**	29
5	**3d**	25
6	**3e**	24

[a]Determined by ^1H NMR analyses using nitromethane as an internal standard.

Next, α,β-unsaturated imides and amide **1b**–**1d** with different auxiliaries were evaluated to clarify their suitability (Table 2). As a result, α,β-unsaturated imide **1b** with pivalamide as the auxiliary was the best substrate among all the other α,β-unsaturated compounds **1a**, **1c**, and **1d**, possessing benzamide, 1,3-oxazolidin-2-one, and 3,5-dimethyl-1*H*-pyrazole, respectively, as their auxiliaries (entries 2 vs. entries 1, 4, and 5). Conducting the reaction in DMF gave a yield similar to that obtained in MeCN (entry 2 vs. entry 3). Thus, we considered that a higher reaction temperature would be necessary to accelerate the intramolecular acylation.[7] We have found out that the generation of α-aminoalkyl radical from **2** under the photosensitized conditions and its subsequent addition to nitrones or imines progressed at room temperature.[4] Being cleaved auxiliaries in situ, they sometimes cause hindrance, such as making it difficult to separate them from the desired products, by their nucleophilic attack on starting materials or products thus decreasing the yield. In this case, we presumed that adding acetic anhydride as a scavenger for the eliminated auxiliaries effectively solves the above problems.[8]

Table 2. Evaluation of auxiliaries and solvents



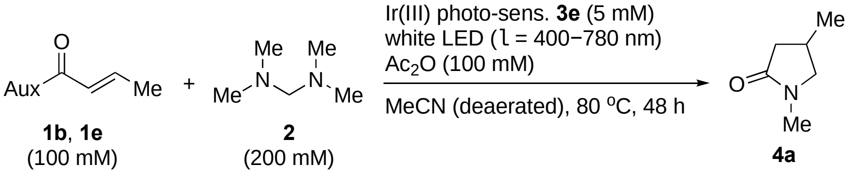
entry	Auxiliary (Aux)	solvent	yield [%][a]
1[b]	 **(1a)**	MeCN	24
2	 **(1b)**	MeCN	34
3	 **(1b)**	DMF	36
4	 **(1c)**	MeCN	28
5	 **(1d)**	MeCN	17

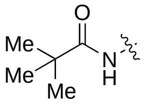
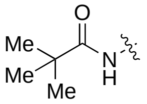
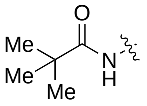
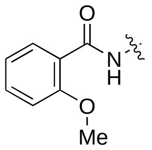
[a]Determined by ^{1}H NMR analysis using nitromethane as an internal standard. [b]The same result is shown in entry 6 of Table1.

Based on this hypothesis, we conducted the formal [3+2] photocycloaddition at 80 °C in the presence of acetic anhydride (Table 3). Additionally, we were concerned about the thermal stability of the Ir(III) complexes **3c**–**3e**. Hence, we re-evaluated Ir(III) complexes **3c**–**3e**. Consequently, the yield of **4a** was improved when compared to the reactions at room temperature (entries 1–3 in Table 3 vs. entries 2 and 3 in Table 2). Eventually, the Ir(III) complex **3e** was found to be the optimal photosensitizer. Furthermore, we used α,β-unsaturated imide **1e**, which our group had previously revealed as a suitable reaction partner of α-aminoalkyl radicals.[9] The reaction of α,β-unsaturated imide **1e** progressed, and 1,4-dimethyl-2-pyrrolidinone (**4a**) was isolated (entry 4 vs. entry 3). Contrary to our expectation, pivalamide or 2-methoxybenzamide, the auxiliary of α,β-unsaturated imide **1b** or **1e**, was obtained as a byproduct instead of acetylated auxiliaries. Pivalamide showed weak UV absorption, and its spot was tailing in TLC analyses.

These observations suggested that it was difficult to isolate **4a** from the reaction mixture containing pivalamide. Eventually, α,β-unsaturated imide **1e** was chosen as the appropriate reagent to isolate **4a** (entry 4).

Table 3. Re-evaluation of Ir(III) complexes and α,β-unsaturated compounds in the presence of Ac_2O under 80 °C

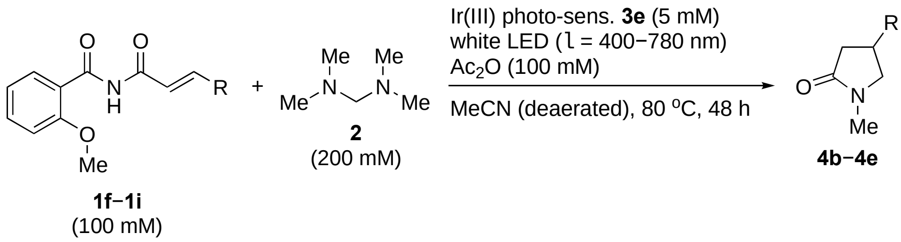


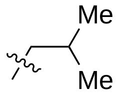
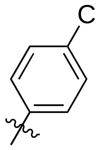
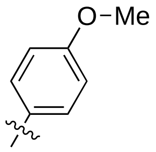
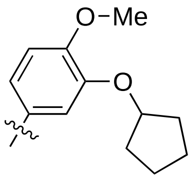
entry	photo-sens.	Auxiliary (Aux)		yield [%][a]
1	**3c**		(**1b**)	65
2	**3d**		(**1b**)	47
3	**3e**		(**1b**)	76
4	**3e**		(**1e**)	74 (51)[b]

[a]Determined by ^{1}H NMR analysis using nitromethane as an internal standard. [b]The yield in parentheses is the isolated yield.

Finally, we investigated the scope of α,β-unsaturated imides **1f**–**1i**, possessing 2-methoxybenzamide as an auxiliary (Table 4). Consequently, the desired 4-alkyl- and 4-aryl-1-methyl-2-pyrrolidinones **4b**–**4d**, and *N*-methylrolipram, **4e** were isolated. However, the yields of **4b**–**4e** were lower than those of **4a** in the reactions of **1b** or **1e** with **2** (Table 3), which implied that bulky substituents decelerated the progress of the reactions. It was difficult to separate **4c** or **4d** with 2-methoxybenzamide, respectively, which forced us to conduct purification several times.

Table 4. Scope of α,β-unsaturated imides

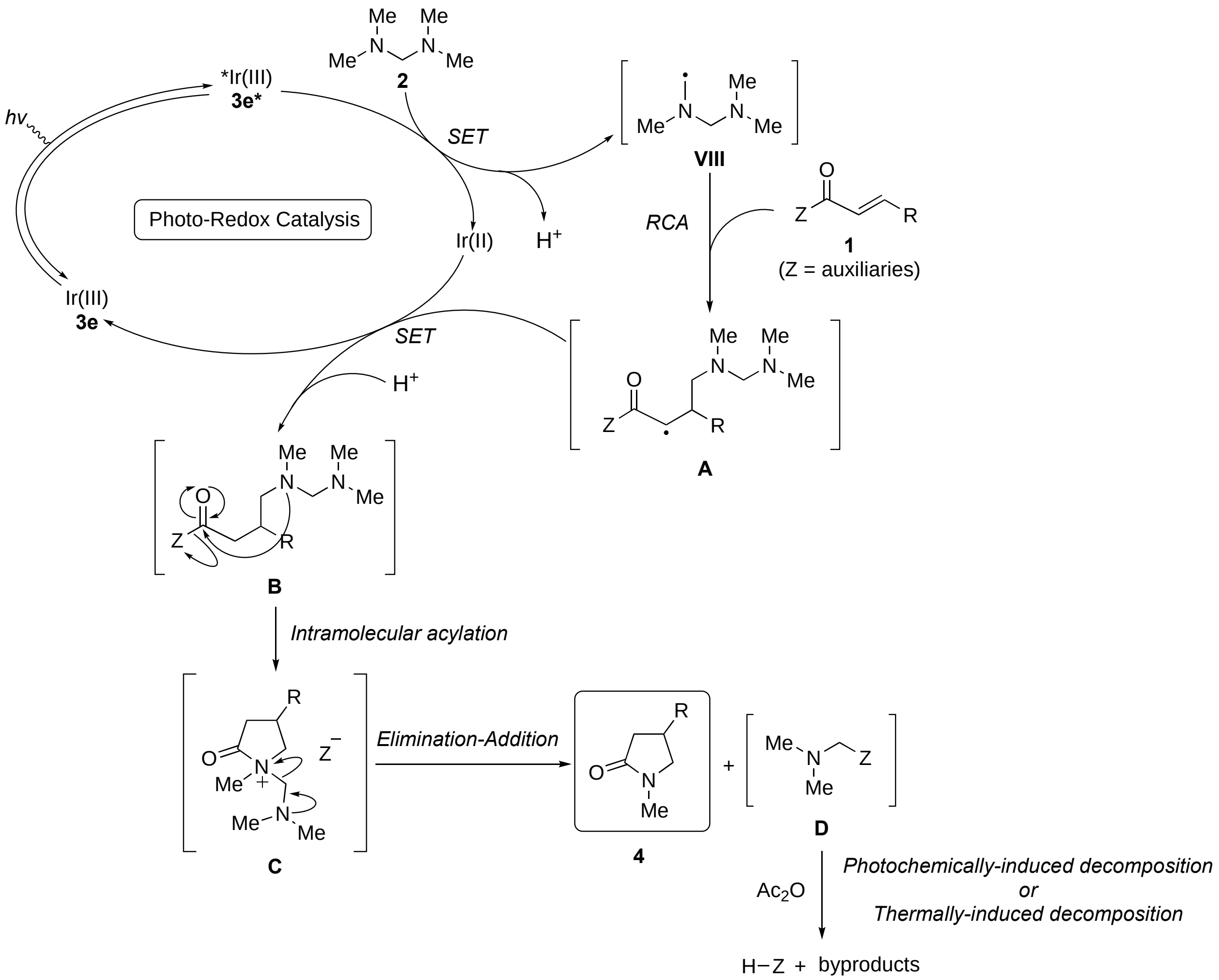


entry	R		yield [%]^{a,b}	
1		(**1f**)	16 (46)^{c}	(**4b**)
2		(**1g**)	4 (21)^{c}	(**4c**)
3		(**1h**)	24 (64)^{c}	(**4d**)
4		(**1i**)	29 (33)	(**4e**)

[a]Isolated yield. [b]Yields in parentheses were determined by ^{1}H NMR analysis. [c]Purification was performed twice.

A plausible mechanism for the photochemical cycloaddition of α,β-unsaturated imides or amide **1** to *N*,*N*,*N'*,*N'*-tetramethyldiaminomethane (**2**) is depicted in Scheme 3. We have reported the Stern-Volmer constants for quenching Ir(III) complex **3e** with α,β-unsaturated imide **1e** as 9.50×10^{-3} M^{-1} and **3e** with *N*,*N*,*N'*,*N'*-tetramethyldiaminomethane (**2**) as 9.62×10^{3} M^{-1}.[4,9] Therefore, the reaction is induced by reductive quenching of the photoexcited Ir(III) complex **3e*** with **2** through SET to generate α-aminoalkyl radical **VIII** and Ir(II) complex. α-Aminoalkyl radical **VIII** is generated regioselectively based on the stereoelectronic rule.[3,4] Subsequently, α-aminoalkyl radical **VIII** reacts with α,β-unsaturated imides or amide **1** through RCA to give α-carbonyl radical **A**. Then, α-carbonyl radical **A** is subjected to SET from the Ir(II) complex, followed by proton transfer[10] to give conjugate adduct **B** and Ir(III) complex **3e**. Subsequently, conjugate adduct **B** undergoes intramolecular acylation to generate ion-pair **C**, which is subsequently converted to the desired 2-pyrrolidinone **4** and putative byproduct **D** through the elimination-addition path. However, we could not identify acetylated auxiliaries. Therefore, it is ambiguous if byproduct

D is decomposed photochemically or thermally in the presence of acetic anhydride to give protonated auxiliary (H–Z) and other byproducts.



Scheme 3. Proposed reaction mechanism

In conclusion, we have developed a formal [3+2] photocycloaddition reaction of α,β-unsaturated imides or amide with *N,N,N',N'*-tetramethyldiaminomethane for the synthesis of 4-alkyl- and 4-aryl-2-pyrrolidinones possessing a methyl group on the nitrogen atom of the 2-pyrrolidinone ring. Further studies are underway to synthesize biologically active compounds containing 4-alkyl and 4-aryl-1-methyl-2-pyrrolidinone scaffolds.

EXPERIMENTAL

Representative Procedure for the Formal [3+2] Photocycloaddition of α,β-Unsaturated Imide 1i with *N,N,N',N'*-Tetramethyldiaminomethane 2

To a test tube equipped with a stir bar were added α,β-unsaturated imide **1i** (45.1 mg, 0.114 mmol, 1.00 equiv.), Ir(III) complex **3e** (6.10 mg, 5.70×10^{-3} mmol, 0.0500 equiv.), acetic anhydride (10.8 μL, 0.114

mmol, 1.00 equiv.), and MeCN (1.14 mL). *N,N,N',N'*-Tetramethyldiaminomethane (**2**) (31.1 μL, 0.228 mmol, 2.00 equiv.) was added to the reaction mixture. The resulting solution was degassed by argon bubbling for 15 min with stirring. The reaction mixture was heated to 80 °C, and then the external irradiation was performed by using a 14W white LED (see SI). The yellowish-brown solution was stirred until **1** was consumed, which was monitored by TLC. Then, volatile compounds were removed by evaporation. The crude product was purified by flash chromatography (stationary phase: spherical silica gel; eluent: 50% EtOAc/*n*–hexane) to afford 9.50 mg (29%) of *N*-methylrolipram **4e** as a pale yellow oil.

SUPPORTING INFORMATION

Supplementary (synthesis of the target molecule, ^{1}H spectra, ^{13}C spectra, etc.) data associated with this article can be found, in the online version, at
URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27768/104/12.

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