

Uncovering New Excited State Photochemical Reactivity by Altering the Course of the De Mayo Reaction

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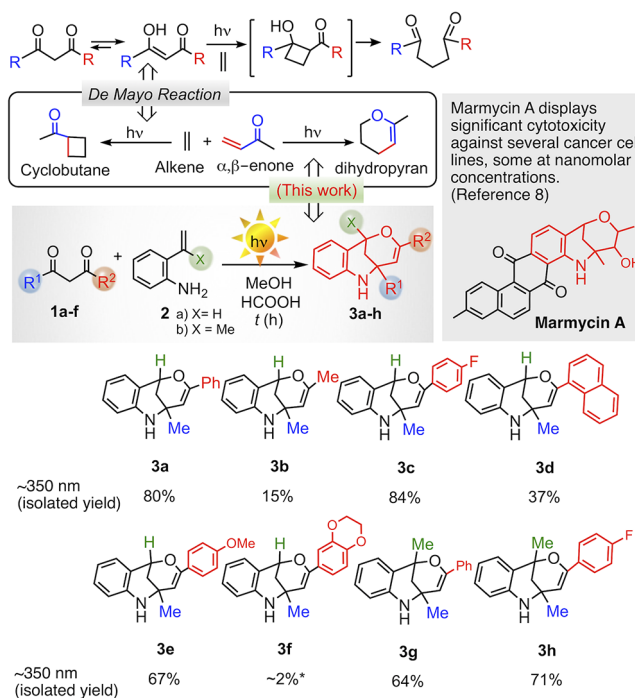
Supporting Information

ABSTRACT: An unprecedented and previously unknown photochemical reactivity of 1,3-dicarbonyl compounds is observed with amino-alkenes leading to dihydropyrans. This novel photochemical reactivity changes the established paradigm related to the De Mayo reaction between 1,3-dicarbonyl compounds and alkenes. This new reaction allows convenient access to the Marmycin core in a single step from commercially available reactants. The origin and scope of this new photoreaction is detailed with preliminary photophysical and mechanistic investigations.

The well-established photoreactivity of 1,3-dicarbonyl compounds with alkenes known as the *De Mayo* reaction^{1,2} has had an epochal impact due to its versatility and has played a seminal role in the development of mechanistic photochemistry, synthetic methodology, and its application to natural product synthesis.^{3–6} The underlying reactivity traits of the *De Mayo* reaction centers around the reactivity of β -hydroxy enone that undergoes a [2 + 2]-photocycloaddition (Scheme 1, top) at the 3,4-position to form a cyclobutane followed by a retro-Aldol ring opening resulting in a 1,5-dicarbonyl skeleton.^{2,3} The *De Mayo* reaction of the corresponding enaminone leads to cyclobutane followed by ring opening/retro-Mannich reaction resulting in ketoimine product(s).^{5,6} This staple reactivity of 1,3-dicarbonyl compounds has not changed in the past six decades. In this report we highlight a new excited state reactivity of 1,3-dicarbonyl compounds with amino-alkene that does not undergo the *De Mayo* reaction but undergoes a new type of excited state transformation leading to dihydropyrans (Scheme 1, top).

Altering the traditional reactivity of a 1,3-dicarbonyl compound requires an intricate understanding of the excited state dynamics involving deactivation pathways and the ability to control the highly reactive intermediate(s) that are formed during the photochemical process.⁷ This necessitates the manipulation of the reactive chromophores to channel their excited state energy toward the desired pathway. In other words, one has to limit the photoactivity along a known reaction trajectory and open a new pathway for excited state deactivation. We envisioned that the photochemistry of 1,3-dicarbonyl compounds can be altered from its traditional reactivity (i.e., *De Mayo* reaction) by having activated alkenes as the reaction partner. This report details the reactivity of 1,3-dicarbonyl compounds with amino-alkenes leading to bicyclo-dihydropyrans (Scheme 1). The reaction showcases how planar reactants can be transformed to bicyclic compounds with complex stereochemistry in one step with the help of light. In addition, the synthesized bicyclic skeleton gives convenient access to the core structure of Marmycin—a marine sediment isolated from a bacterium related to the

Scheme 1. Evaluating Photocycloaddition of 1,3-Dicarbonyl Compounds with Amino-Alkenes^a



^aIsolated yields of photoproduct and *NMR yield of 3f are provided. Refer to the SI for irradiation conditions.

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*Streptomyces*⁸ that shows cytotoxicity against several cancer cell lines (Scheme 1). Marmycins are cytotoxic quinones previously synthesized by multistep thermal reactions.⁹

We began our evaluation of the photoactivity of commercially available 1-phenyl-1,3-butanedione **1a** with amino-styrene **2a** (Scheme 1). A methanolic solution of 1-phenyl-1,3-butanedione **1a** in the presence of formic acid (catalytic amounts) was stirred with **2a** for 4 h and deoxygenated with N₂ purging. Irradiation of this deoxygenated mixture at ~350 nm for 6 h resulted in 80% isolated yield of the photoproduct **3a** (Scheme 1). The photoproduct was purified by column chromatography and was characterized by various analytical techniques.¹⁰ We were able to successfully crystallize the photoproduct **3a** and unambiguously ascertain its structure by single crystal XRD.¹⁰ To expand on the scope of the reaction, we systematically varied the substituents on the 1,3-diketone **1a–f** to understand the structural features that are responsible for the observed photoreaction. Inspection of Scheme 1 shows that the reaction can be accomplished with dicarbonyl compounds **1a–f** featuring alkyl or aryl groups with amino-styrene **2a**. The conversion was dependent on the absorbance of the reactant(s) as the pentane-2,4-dione **1b** (methyl instead of a phenyl substitution on the 1,3-dicarbonyl unit) gave a lower yield of 15% of the corresponding photoproduct **3b** (Scheme 1). Electron withdrawing *para*-fluoro substituted 1,3-dicarbonyl compound **1c** gave 84% isolated yield of **3c**. Irradiation of **1e** featuring electron-donating methoxy substituent gave 67% isolated yield of **3e**. Increasing the electron rich nature of the aryl ring (**1f**) resulted in a trace (~2%) amount of the corresponding photoproduct **3f**. Irradiation of **1d** featuring a naphthyl substituent resulted in 37% isolated yield of **3d**.

We also extended our investigation by altering the amino-styrene functionality to gauge its influence on the observed reactivity (Scheme 1). Irradiation of dione **1a** with α -methyl substituted-amino-styrene **2b** resulted in the corresponding dihydropyran photoproduct **3g** with 64% isolated yield. Comparison of reactivity of **2a** and **2b** with dione **1a** reveals that the isolated yield of photoproduct was lowered upon α -substitution from 80% (for **2a**) to 64% (for **2b**). While α -substitution lowered the yield, there was a noticeable enhancement of reactivity under identical conditions as the irradiation time was significantly shorter with **2b** compared to **2a**. For example, 6 h irradiation was necessary with styrene **2a** and dione **1a** and **1c**, while 1–2 h irradiation was required with styrene **2b** for comparable isolated yields (**3h**: 71% vs **3c**: 84% and **3g**: 64% vs **3a**: 80%).

A change in the absorption profile (Figure 1) was observed when **1a** was stirred with **2a** in MeOH (stirred for 4 h). Analyzing the mixture **1a** with **2a** (stirred for 4 h in MeOH) by ¹H NMR spectroscopy revealed the formation of enaminone **4a**.¹⁰ To verify this, we independently synthesized (by conventional heating or by microwave irradiation)¹⁰ enaminone **4a** and characterized it by various analytical techniques.^{11,12} ¹H NMR spectroscopic analysis of the synthesized reaction mixture showed the presence of both the *Z*-isomer and *E*-isomer of **4a**.¹⁰ Heating the reaction mixture to 85 °C for 10 min resulted in the formation of *Z*-**4a** as the major isomer.¹⁰ The enaminone was purified by column chromatography (*Z*:*E* ratio = 1:0.05 by ¹H NMR spectroscopy).¹⁰ This composition indicated that *Z*-isomer is thermodynamically more stable than the corresponding *E*-isomer likely due to intramolecular hydrogen bonding. The presence of intra-

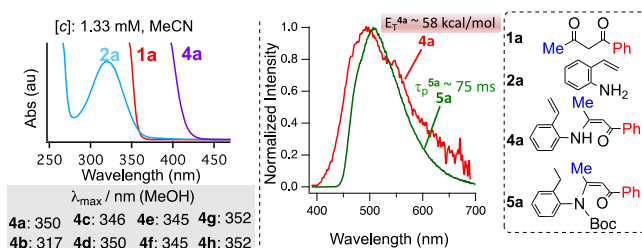
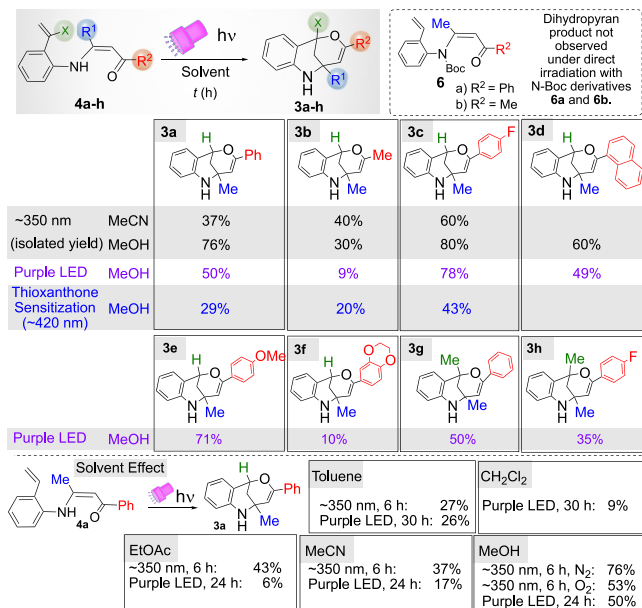


Figure 1. Left: UV-vis absorption profile of **1a**, **2a**, and **4a** in acetonitrile and the absorbance maxima of **4a–h** in MeOH. Right: Time-resolved phosphorescence spectra of **4a** and **5a** in ethanol glass at 77 K ($\lambda_{\text{ex}} = 360$ nm) with 10–30 ms detection window after light pulse.

molecular hydrogen bonding in the *Z*-isomer was further established from the single crystal XRD of **4a**.¹⁰ UV-vis spectra of **4a** displayed the onset of absorptivity in the visible region when compared to **1a** and **2a** (all at $c = 1.3$ mM in acetonitrile; Figure 1, left). In addition, the onset of absorptivity in **4a** showed that it can be selectively excited in the presence of **1a** and **2a** (precursors for **4a** synthesis). On the basis of these observations, the photoreaction between 1,3-diketones **1a–f** and the amino-alkenes **2a,b** likely proceeds via an in situ generated enaminone **4a–h** (Schemes 1–2), leading to the observed photoproduct **3a–h**.

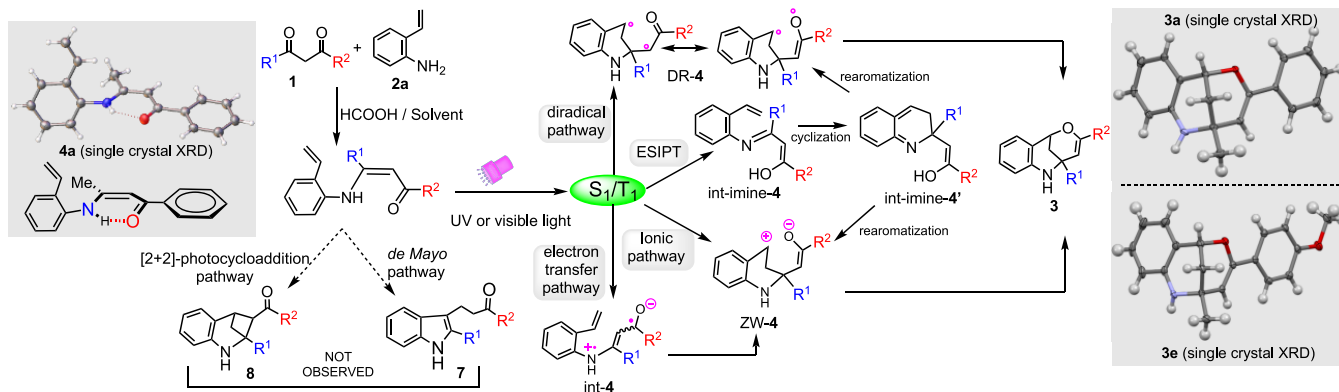
Scheme 2. Photoreactivity of Enaminones **4a–h** under Various Conditions^a



^aFor purple LED irradiations the yields are from ¹H NMR spectroscopy with triphenylmethane internal standard. Isolated yields for ~350 nm irradiations. Refer to the SI for irradiation conditions.

As in situ generated enaminone **4** (Schemes 1 and 2) was responsible for the observed photoreactivity between 1,3-diketones **1a–f** and the amino-alkenes **2a,b**, we evaluated the photoreactivity of **4a** as a model system (Scheme 2). Irradiation of **4a** in methanol (0.02 mM) at ~350 nm resulted in a clean and efficient reaction (clean reaction was observed by ¹H NMR spectroscopic analysis of crude mixture)¹⁰ leading to photoproduct **3a** in 76% yield (Scheme 2). It is striking to

Scheme 3. Mechanistic Features of Photocycloaddition of 1,3-Dicarbonyl Compounds with Amino-Alkenes



note that irradiation of **4a** in methanol gave 76% isolated yield (Scheme 2) and irradiation of the mixture of **1a** and **2a** under similar conditions gave 80% isolated yield (Scheme 1). This once again reinforced our conjecture that enaminone **4a** was likely responsible for the observed reactivity upon irradiation of 1,3-dicarbonyl compound **1a** and amino-styrene **2a** (Scheme 1). Control studies in the absence of light (thermal control) led to the recovery of enaminone **4a**.¹⁰ To further understand the reactivity patterns, the photoreactivity of enaminone **4a** leading to the photoproduct **3a** was investigated under various conditions (Scheme 2). Two distinct aspects were specifically evaluated viz., role of the solvent and irradiation wavelength. As expected, the photoreaction was faster at ~350 nm, compared to purple LED irradiation (Scheme 2) due to the difference in the optical density of the substrate at a given concentration. Consequently, longer reaction times were employed for purple LED irradiations for achieving similar conversions as ~350 nm irradiation. The phototransformation was clean and efficient in methanol at ~350 nm with 76% isolated yield of photoproduct **3a** (**3a** observed exclusively in crude ¹H NMR spectroscopy).¹⁰ The reaction was also observed to be clean and efficient with purple LED albeit with longer irradiation times. Moderate yield of **3a** was observed in other solvents viz. 37% yield in acetonitrile, 43% yield in ethyl acetate and 27% yield in toluene (Scheme 2).

To generalize the observed reactivity leading to photoproduct **3**, we investigated the reactivity of enaminones **4b–h** which were independently synthesized from the corresponding diketones **1b–f** and **2a,b** (Scheme 2), respectively.¹⁰ Irradiation at ~350 nm in acetonitrile resulted in isolated yield of 40% for **4b** and 60% for **4c**. Changing the solvent to methanol resulted in isolated yield of 30% for **4b**, 80% for **4c**, and 60% for **4d**. Purple LED irradiation of enaminone **4b–f** in methanol gave the photoproduct **3b–h** in yields varying from 9 to 78% (9% for **4b**, 78% for **4c**, 49% for **4d**, 71% for **4e**, 10% for **4f**). The dialkyl substituted enaminone **4b** gave lower conversions because its absorptivity was weak in the visible region. Irradiation of enaminones **4g** and **4h** featuring α -methyl substituted-amino styrene unit gave the corresponding photoproducts **3g** and **3h** in 50% and 35% yields, respectively (Scheme 2). A point to note is the reaction efficiency with enaminones featuring α -methyl substituted-amino styrene (30 min to 1 h irradiation with purple LED) was more efficient than enaminones derived from **2a** (24–48 h irradiation with purple LED) highlighting the role of the substitution on the styrenyl unit.

To understand the observed reactivity, preliminary photophysical studies were performed on enaminones to understand their excited state properties. We utilized enaminone **4a** as a model compound. There was no observable fluorescence of **4a** at room temperature (fluorescence quantum yield <0.001), that indicated fast excited state deactivation processes. Time resolved luminescence measurements of **4a** at 77 K in ethanol glass revealed a weak phosphorescence centered around 490 nm (Figure 1, right; red). This weak phosphorescence limited the ability to ascertain the excited state lifetime of the triplet state. To overcome this limitation, we synthesized the control substrate **5a** (lacking the alkenyl substituent on the phenyl ring with N-Boc protection) that displayed phosphorescence similar to **4a** albeit with higher intensity with a lifetime of ~75 ms (Figure 1, right).¹⁰ This showed that the triplet was localized on the enaminone functionality. We believe that the fast relaxation of the excited state of **4a** can have its origin in distinct deactivation modes viz., (a) isomerization of the double bond, and/or (b) excited state intramolecular proton transfer (ESIPT), and/or (c) charge transfer in the excited state (as it is a push–pull system). Our photophysical studies revealed that the triplet excited state energy of **4** to be around 58 kcal/mol above the ground state. This enabled us to utilize thioxanthone ($E_T \sim 64$ kcal/mol) as sensitizer/photocatalyst to carry out the transformations. Irradiation of enaminones **4a–c** in the presence of thioxanthone at ~420 nm for 48 h resulted in the dihydropyran photoproducts with yields of 29% of **3a**, 20% for **3b**, and 43% for **3c** (Scheme 2). In the absence of thioxanthone, irradiation of **4b** at ~420 nm for 44 h did not show any appreciable photoproducts (<2% conversions).¹⁰ This indicated that the reaction can also be performed under photocatalytic conditions.¹⁰ As electron-transfer initiated reactivity was endergonic¹⁰ based on the redox potentials of enaminone **4** and thioxanthone,^{13,14} the photoreactivity under sensitized/photocatalytic conditions occurs likely via an energy transfer process (Scheme 2).

On the basis of our photochemical and photophysical investigations, we propose a preliminary mechanistic model for the observed reactivity (Scheme 3). Irradiation of diketone **1** and amino-styrene **2**, results in the excitation of in situ generated enaminone **4**. The photoexcited enaminone can react either through a singlet or triplet manifold via four distinct pathways (Scheme 3) viz., (i) a diradical pathway; (ii) an ionic pathway; and (iii) an electron transfer pathway or (iv) an excited state intramolecular proton transfer (ESIPT) pathway^{15–17} leading to **3**. The reaction pathway depends on the substrate(s) and the employed conditions for the

transformation. The Boc substituted derivatives **6a,b** did not give the corresponding dihydropyran photoproduct under direct irradiation (Scheme 2).¹⁰ This indicated that the excited state proton transfer or an excited state charge transfer (from singlet or triplet excited state) plays a crucial role in the observed phototransformations. The single crystal XRD structure of **4a** (Scheme 3) showed that the Z-isomer of **4a** is stabilized by intramolecular H-bonding.¹⁰ Hence, direct excitation of **4** resulting in ESIPT is one of the likely pathways that generates int-imine-4,^{15–17} followed by cyclization and rearomatization leading to a zwitterion ZW-4 that subsequently results in the photoproduct **3**. Indirect evidence for the ESIPT mechanism comes from photophysical studies where we observed no luminescence at room temperature suggesting fast deactivation processes. There are two excited state processes that one can envision for this fast deactivation in **4** viz., photoisomerization and ESIPT.⁷ As we observe an extremely weak phosphorescence for **4a** at 77 K (Figure 1, right), excited state decay due to photoisomerization can be ruled out in favor of ESIPT due to the rigid nature of the matrix. In addition, noticeable phosphorescence with a lifetime of ~75 ms from the ethyl substituted Boc-derivative **5a** points to a fast deactivation in **4** that has its origin in ESIPT mediated process. As the reaction worked under sensitized irradiation/photocatalytic conditions, the reaction might also proceed via a diradical pathway involving DR-4 (triplet diradical) en route to the photoproduct **3**. Under direct irradiation the observed reactivity/product yields under oxygen and nitrogen atmospheres were comparable (Scheme 2) that indicated that the excited state(s) (even if they are in the triplet manifold) are too short-lived to be quenched by oxygen (albeit scavenging of reactive intermediates is still feasible). Under photocatalytic conditions, based on the redox potentials of the enaminone and photocatalyst (thioxanthone),¹⁰ the electron transfer pathway is likely not feasible,^{13,14} and the reaction likely occurs via an energy transfer process.

Our study showcases the immense potential of excited state transformations as platforms to uncover new reactivity and to access structurally complex skeletons. Detailed spectroscopic studies coupled with excited state dynamics are currently being investigated to understand the complexities of this newly uncovered photoreaction for expanding its utility and scope.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.0c12099>.

Experimental procedures, characterization data, analytical conditions, and photophysical studies (PDF)

Accession Codes

CCDC 2034200, 2035217, 2035796, and 2059514 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

S.K.K. and L.K.V. contributed equally, are considered co-first authors, and are listed in alphabetical order of their last names.

Notes

The authors declare no competing financial interest.

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