Journal Name

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Reinventing the De Mayo Reaction: Synthesis of 1,5-Diketones or 1,5-Ketoesters via Visible Light [2+2] Cycloaddition of β-Diketones or β-Ketoesters with Styrenes

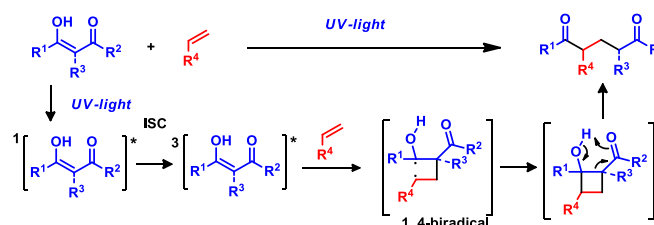Rebeca Martinez-Haya[b], Leyre Marzo*[a] and Burkhard König*[a]

A visible light mediated De Mayo reaction between 1,3-diketones and styrenes following a [2+2] cycloaddition pathway *via* photosensitization mechanism give access to 1,5-diketones. The reaction has been applied to substituted styrenes and aryl- and alkyl-substituted ketones. Moreover, the method converts β-ketoesters, β-amido esters, and β-cyano ketones. Seven membered rings, a frequent structural motif of natural products, are also accessible by this methodology.

The photochemical reaction between β-diketones and double bonds under UV light irradiation is known as the De Mayo reaction.[1] In 1962 Paul Jose De Mayo reported that the enolic form of a 1,3-diketone can undergo a [2+2] photocycloaddition with an olefin under UV irradiation affording a non-isolable cyclobutanol intermediate that evolves through a retro-aldol reaction yielding 1,5-diketones (Scheme 1). However, it was not until the late 1970s that its synthetic utility was fully realized when, *via* the intramolecular version, more complex macrocyclic structures became accessible.[2] Examples are the total synthesis of (±)-ingenol[3] or the alkaloid mesembrine[4] that employ the De Mayo reaction as the key step, or the formal synthesis of vindorosine,[5] among others.[6] In these reactions the β-diketone is directly excited by UV irradiation to its singlet excited state, which undergoes intersystem crossing to the excited triplet (Scheme 1). Further complexation of the triplet state with the double bond forms an exciplex that evolves to form the most stable 1,4 biradical. This 1,4-biradical generates the cyclobutanol intermediate that affords the desired products (Scheme 1).[7a] However, to the best of our knowledge a sensitized version of this reaction allowing the use of visible light has not been reported so far.[7]

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Scheme 1. De Mayo photocycloaddition

Over the last decade, visible light photocatalysis[8] has developed into an important tool in synthesis. The lower cost and energy demand of the visible light sources, together with the selective excitation of the photocatalyst, thus avoiding undesired pathways, are some of the advantages. Photoredox catalysis has afforded several approaches for the [2+2] photocycloaddition between double bonds or Michael acceptors via photosensitization.[9] In particular, Yoon reported the intramolecular [2+2] photocycloaddition of styrene derivatives by direct photosensitization using an iridium complex as photosensitizer of the reaction under visible light irradiation.[9a] Based on this precedent, we envisaged that a visible light De Mayo reaction may be possible *via* the photosensitization of the styrene by the photocatalyst through energy transfer, triggering the [2+2] photocycloaddition with the enol of a 1,3-diketone to obtain the desired 1,5-diketones.

To prove this hypothesis, a solution of styrene **2a** and 1,3-diphenylpropane-1,3-dione **3a** in the presence of 2 mol% [Ir(dF(CF$_3$)ppy)$_2$(bpy)]PF$_6$ **1a**, in CH$_3$CN was subjected to blue LED irradiation over 20 h, affording the 1,5-diketone **4a** in 69% yield (entry 1, Table 1). Then, different catalyst with different oxidation power (see scheme in Table 1)[10] were tested in the reaction. Ru(bpy)$_3$Cl$_2$ **1b**, Ir(ppy)$_3$ **1c** and Mes-Acr$^+$ **1e** did not react, while the carbazol derivative **1d** afforded the desired product in 44% yield (entries 2-5, Table 1). Taking into account that the enol of **3a** is the reactive species, tributylmethylammonium dibutyl phosphate was tested in the reaction, in order to shift the keto-enol equilibria to the enol form, obtaining **4a** in 79% yield (entry 6, Table 1). Control

reactions revealed that both the catalyst and light are necessary for the reaction (entries 7 and 8, Table 1). Finally, the use of the polar protic solvent EtOH improved the yield to 96% (entry 7, Table 1). Therefore, the optimized conditions are: **1a** (2 mol %), **2a** (5 equiv.), **3a** (1 equiv.), $(BuO)_2P(O)ONBu_3Me$ (25 mol %), EtOH (1 mL), N_2, 25 ºC, 455 nm (for further details see Table S1, SI).

**Table1.** Optimization of the reaction conditions for the photosensitized De Mayo reaction.[a]
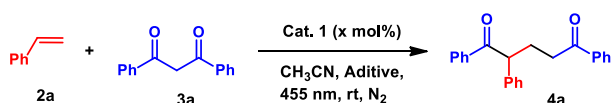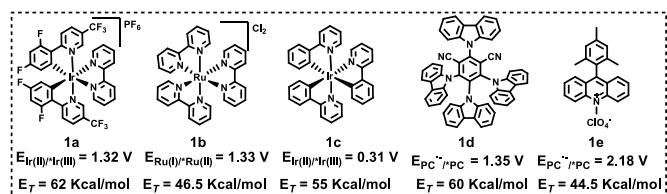
Entry	Cat (mol%)	Additive (25 mol%)	Solvent	Yield (%)[b]
1	**1a** (2)	--	CH_3CN	69
2	**1b** (3)	--	CH_3CN	0
3	**1c** (2)	--	CH_3CN	0
4	**1d** (4)	--	CH_3CN	44
5	**1e** (4)	--	CH_3CN	0
6	**1a** (2)	$(BuO)_2P(O)ONBu_3Me$	CH_3CN	79
7	**1a** (2)[c]	$(BuO)_2P(O)ONBu_3Me$	CH_3CN	0
8	--	$(BuO)_2P(O)ONBu_3Me$	CH_3CN	0
9	**1a** (2)	$(BuO)_2P(O)ONBu_3Me$	EtOH	96

[a] The reactions were performed with 0.1 mmol of **3a**, 0.5 mmol of **2a**, and 1 mL of CH_3CN. [b] Isolated yields after 20h. [c] Without light.

With the optimized conditions in hand, we proceed to study the scope of the reaction between the β-diketone **3a** and different styrene derivatives **2** (Table 2). Styrenes bearing electron donating or electron withdrawing groups in the *ortho*, *meta* or *para* position yielded the final products in good to very good isolated yields (**4a-f**, Table 2). Therefore, the electronic nature of the substituents does not seem to have a big impact in the reaction. The reaction could be also performed in a 1 mmol scale of **3a** using a different set up (see SI Figure S11), obtaining **4a** in 66 % yield, thus proving the robustness of the methodology (Table 2). More hindered styrene derivatives also underwent this reaction satisfactorily. Thus, α-methyl styrene afforded **4g** in a moderate 56% yield, while dialin yielded **4h** as single stereoisomer in very good yield (Table 2). The reaction was also performed with the *E/Z*-mixture of isoeugenol that afforded **4h** as single diastereoisomer. This stereoselectivity can be explained attending to the fast (*E*)/(*Z*) geometric isomerization of the triplet alkenes, and assuming that only the (*E*)-isoeugenol would react in a stereoconvergent manner.[9a] Alkyl substituted double bonds such as

cyclohexene or 1-methyl-1-cyclohexene did not react (**4j** and **4k**, Table 2). This lack of reactivity is due to the higher triplet energy of these compounds (see mechanistic proposal).[11] (Isopropenyloxy)trimethylsilane afforded the desired product in good yield (**4l**, 52% yield, Table 2). Next, we studied the scope of the reaction between β-diketones **3** with styrene **2a** (Table 2). First, differently substituted 1,3-diketones were studied. Under the optimized reaction conditions, aromatic diketones bearing electron withdrawing or electron donating substituents in the aromatic ring reacted smoothly, affording the desired products **4m-p** in good to excellent yields (Table 2). Alkyl substituents are also tolerated in the reaction, but in this case slightly different reaction conditions are required: compound **4q** is obtained in excellent yield when 4 mol% of **1d** is used as catalyst in CH_3CN as solvent (conditions B, Table 2). The steric hindrance afforded by the *t*-Bu or the methyl group in the reactive methylene completely suppress the reactivity (**4r** and **4s**, Table 2).

Table 2. Scope of the reaction between different styrene derivatives **2** and β-EGW-substituted ketones **3**.[a]
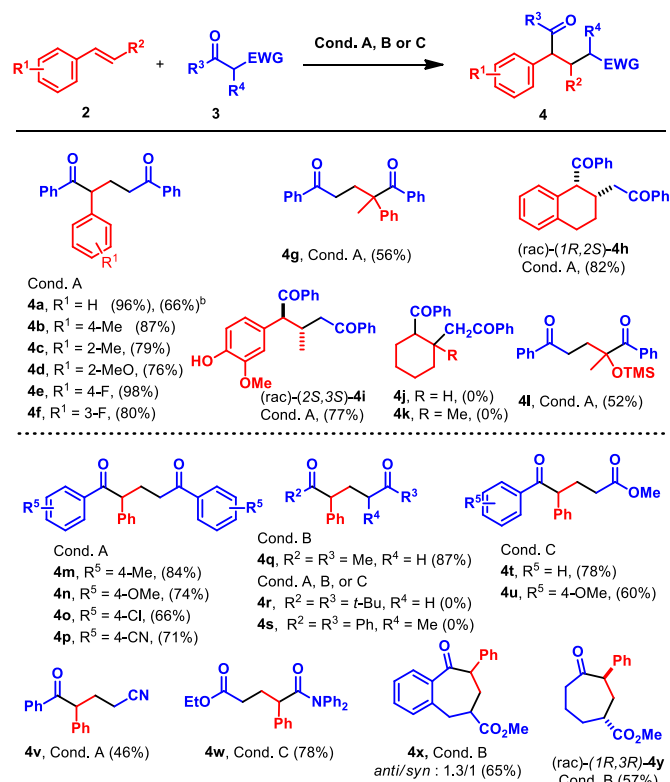
[a] All reactions were carried out using 0.1 mmol **3**, 0.5 mmol **2a** and the reaction conditions indicated in each case. *Reaction conditions A*: 0.002 mmol $Ir[dFCF_3ppy]_2(bpy)PF_6$ **1a**, 0.025 mmol n-$Bu_2PO_4NMe(n$-$Bu)_3$, EtOH, N_2, 25 ºC, 455 nm; *Reaction conditions B*: 0.004 mmol 4CzIPN **1d**, 0.025 mmol n-$Bu_2PO_4NMe(n$-$Bu)_3$, CH_3CN, N_2, 25 ºC, 455 nm; *Reaction conditions C*: 0.004 mmol 4CzIPN **1d**, 0.1 mmol K_2CO_3, CH_3CN, N_2, 25 ºC, 455 nm; [b] Reaction carried out with 1 mmol **3a**, 5 mmol **2a** , 0.02 mmol $Ir[dFCF_3ppy]_2(bpy)PF_6$ **1a**, 0.25 mmol n-$Bu_2PO_4NMe(n$-$Bu)_3$, EtOH (10 mL), N_2, 25 ºC and 455 nm LED.

We extended the reaction scope to other ketones bearing different electron withdrawing substituents in the β-position. β-Keto esters also underwent this reaction, but a combination of 1 equivalent of a

stronger base (K_2CO_3) and 4 mol% **1d** in CH_3CN was necessary to obtain **4t** and **4u** in good yields (conditions C, Table 2). β-Cyano ketones reacted under the standard conditions giving **4v** in moderate 46% yield, while from a β-amido ester, **4w** was isolated in 78% yield using reaction conditions C (Table 2). To prove that the reaction could be applied for the synthesis of larger ring systems, such as compounds bearing 7 membered rings,[12] the reaction was performed with cyclic β-keto esters. Thus, under reaction conditions B, **4x** was obtained as a diasteromeric mixture 1.3:1 of the (rac)-(6*S*,8*R*) and (rac)-(6*R*, 8*R*) δ-keto esters in good yield, while **4y** was isolated as single regioisomer in good yield (Table 2).

Then, the elucidation of the reaction mechanism was attempted, considering either an electron transfer or an energy transfer as the initial step of the reaction. Tobita et al. reported that, in solution, **3a** exist mainly as the enol form,[13] therefore, this will be the initial reactive species considered for the reaction mechanism. Regarding the radical mechanism an initial oxidation step was considered. The oxidation potentials of the three initial species are 1.43 V for **3a** (see Figure S5, SI), 1.97 V for **2a**,[14] and 0.6 V *vs* SCE for the enolate of **3a** (H-NMR experiments revealed the presence of enolate in solution in the presence of base, see SI, section 5 and Figure S7 for the CV). Reported redox potentials for the photocatalysts, which afford the final products, are 1.32 V and 1.35 V *vs* SCE for **1a** and **1d**, respectively (see Table 1).[10] Thus, in principle, an electron transfer reaction (photoredox) between any of the photocatalyst and the enolate of the β-diketone could be thermodynamically favoured, but it would not be favoured in the case of an electron transfer with the styrene (see SI, Table S2). With this assumption, photocatalyst **1e**, with a redox potential of 2.18 V *vs* SCE[10f, g] should even work better than the active ones. However no product formation was observed when using **1e** (Table 1, entry 5). Besides, previous studies form Sharp[15] revealed that the radical reaction between β-diketones and double bonds under oxidative conditions affords linear α-substituted β-diketones,[16] while the De Mayo reaction (photochemical conditions) yields the 1,5-diketone derivative.[17] Under these precedents, a photocycloaddition pathway promoted by photosensitization is more likely than a radical pathway promoted by oxidation of the β-diketone.

Regarding the photosensitization mechanism, the excited photocatalyst can transfer the energy either to **2a** or to **3a** (Scheme 2). According to the triplet energy values ($E_{T(enol-3a)}$ = 59 Kcal/mol[18a]; $E_{T(2a)}$ = 60 Kcal/mol[9a]; $E_{T (1a)}$ = 62 Kcal/mol[10a]; $E_{T(1d)}$ = 60 Kcal/mol[10e]), sensitization[19] of the enol-**3a** or styrene **2**, with triplet energies in the range of **1a**, is feasible. This statement was corroborated by the efficient quenching observed in the time resolved luminescence quenching experiments of **1a*** with **2a** and **3a** (See SI, figures S2 and S3). In addition, the lack of reactivity in the reactions with photocatalysts that are well known photosensitizers[20] such as $Ru(ppy)_3Cl_2$ **1b** (E_T = 46.5 Kcal/mol[10b, c]), $Ir(ppy)_3$ **1c** (E_T = 55 Kcal/mol[10d]) or **1e** (E_T = 55 Kcal/mol[10f]), but whose triplet energies are below the triplet energies of **2a** and **3a** support an energy transfer as the most likely mechanism (see SI, section 4). Therefore, our proposed mechanism starts with the excitation of the photocatalyst by irradiation with blue light, followed by energy transfer to **2a** or **3a**, reaching the triplet excited state ³(**2a**)* or ³(**3a**)*.

Then, ³(**2a**)* reacts with **3a**, while ³(**3a**)* would react with **2a**, leading to a common 1,4-biradical intermediate **I**, with the radicals in the most stable positions (α to the OH and in the benzylic position), explaining the observed regioselectivity of the final products. From this biradical intermediate, cyclobutanol **II** is generated, followed by retro aldol condensation affording the final product **4a** (Scheme 2).
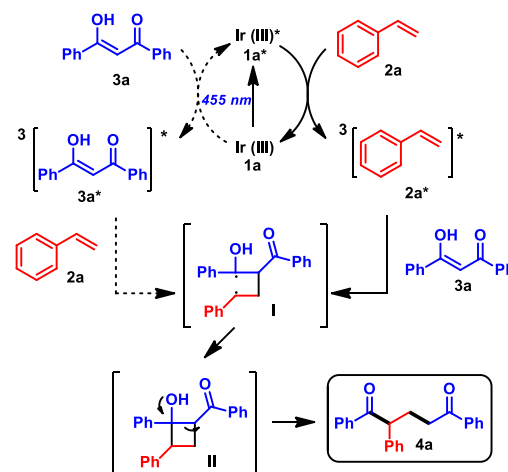
Scheme 2. Visible light mediated photosensitized approach of the De Mayo photocycloaddition

According to the time resolved luminescence quenching experiments it is difficult to elucidate whether the energy transfer to styrene **2a** or **3a** would be predominant. However, **2a** is 5 times more concentrated in the reaction mixture than **3a**, thus energy transfer to **2a** seems more likely. In addition, GC-MS analysis (see SI, Figure S10) of the reaction between **3a** and **2a** under optimized conditions (entry 9, Table 1) revealed the formation of the dimerization product of styrene[9c] as side product of the reaction. On the other hand, the lack of reactivity with cyclohexene derivatives (**4j**, **4k**, Table 2) that present triplet energies around 80 Kcal mol⁻¹ suggested that photosensitization of **3a** is not enough to trigger the reaction (time resolved luminescence quenching experiment of **1a** with cyclohexene shows no interaction between **1a*** and the olefin, see SI, Figure S4). Therefore, although photosensitization of **3a** cannot be discarded as a possible mechanistic pathway, all those indirect proves indicated photosensitization of styrene **2a** as the predominant pathway under this reaction conditions. Finally, the quantum yield of the reaction was determined to be *Φ* = 1.1%, suggesting that the mechanism does not contain significant radical chains.[21]

In conclusion, the first visible light mediated De Mayo reaction through a photosensitization mechanism has been developed. α or β-substituted styrenes undergo smoothly this reaction, but the higher triplet state energy of alkyl substituted olefins made them unreactive under this conditions. β-diketone, β-ketoester, β-cyano ketone and β-amido ester derivatives could be successfully functionalized and 7 membered rings are readily accessible by this method. Mechanistic studies support photosensitization as the key step of the reaction, and experimental observations suggested photosensitization of styrene as the most likely mechanistic pathway.

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Conflicts of interest

Acknowledgements

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