Synthesis of $\varepsilon$-oxo acids by photostimulated reactions of 2-(2-iodophenyl)acetate ion with carbanions by the S$_{RN1}$ mechanism. Synthesis of novel 3-benzazepin-2-ones

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Abstract

The synthesis of 3-benzazepin-2-ones using commercially available 2-(2-iodophenyl)acetic acid as starting material is described. The synthetic strategy involves the S$_{RN1}$ substitution reaction in DMSO as solvent under photoinitiation, using ketone enolate ions as nucleophiles to obtain $\varepsilon$-oxo acids, followed by a condensation reaction of $\varepsilon$-oxo acids with ammonium acetate in glacial acetic acid to produce novel 3-benzazepin-2-ones. The target compounds are afforded in regular to good yields and the factors governing the distribution of substitution products are discussed.

Keywords: 3-Benzazepin-2-ones, $\varepsilon$-oxo acids, S$_{RN1}$ reactions, ketone enolate ions, electron transfer, photochemistry

Introduction

The $\gamma$-, $\delta$-, and $\varepsilon$-oxo acids constitute valuable building blocks for the asymmetric synthesis of several carbo- and heterocycles including 4,4-disubstituted-1-naphthalenones,\textsuperscript{1} pyrrolidines,\textsuperscript{2} piperidones,\textsuperscript{3} azepines\textsuperscript{4} and 3-benzazepines.\textsuperscript{4} However, a few methods with modest yields are available for their preparation. Recently, $\varepsilon$-oxo acids were synthesized from the diacid $o$-phenylenedicarboxylic acid with organolithium (RLi, R = Me, Et, $n$-Bu, Ph) in regular to good yields (35-55\%).\textsuperscript{5} In this case, the selective formation of $\varepsilon$-oxo acids as the main product is based on the intermediate formation of a hemiketal anion.

Seven-membered nitrogen heterocyclic compounds are important target molecules due to their frequent occurrence in a number of bioactive natural products and therapeutic agents.\textsuperscript{6} For
example, benzazepinones are ubiquitous structural units found in a large array of natural products and pharmaceuticals, with a broad spectrum of biological activity for the treatment of cardiovascular diseases, tumors, etc. Thus, the synthesis of these compounds has been subject of intensive study.

The regioselective synthesis of 3-benzazepin-2-ones has been recently reported by the intramolecular addition of amides to alkynes by palladium-catalyzed or Au(PPh3)Cl /AgSbF6-catalyzed reactions with high regioselectivity and moderate to good yields.

The unimolecular radical nucleophilic substitution, or S_RN1 reaction, is a process through which an aromatic nucleophilic substitution could be achieved. This mechanism is an important route in order to achieve the formation of new C-C bonds by the reaction of aromatic substrates with carbanions. Good yields of substitution are usually obtained in these reactions with both aliphatic and aromatic ketone enolate ions. These anions react with aromatic halides under photostimulation in liquid ammonia (NH3(l)) or in DMSO as solvents. Since the scope of this process has increased considerably over the last decades, nowadays it serves as an important synthetic strategy for heterocycles.

The S_RN1 mechanism is a chain process. The initiation step (equation 1) is an electron transfer (ET) from a suitable donor (generally the nucleophile) to the substrate, to afford a radical anion. In some of these systems the ET step is spontaneous; however, in others, light is required to catalyze the reaction. Electrons (from dissolution of alkali metals in NH3(l) or from a cathode) and inorganic salts (Fe^{2+}, SmI2) can initiate the reaction as well. The propagation steps consist of the fragmentation of the radical anion, to yield a radical and the nucleofugal group (equation 2). The coupling of the radical with the nucleophile affords the radical anion of the substitution product (equation 3). This intermediate is necessary to continue the propagation cycle as it forms the radical anion of the substrate by ET (equation 4). Overall, eqs 2-4 depict a nucleophilic substitution (equation 5) with radicals and radical anions as intermediates.

\[
\begin{align*}
\text{Initiation Step} & \\
\text{ArX} + \text{Electron Donor} & \rightarrow (\text{ArX})^\cdot & (1) \\
\text{Propagation Steps} & \\
(\text{ArX})^\cdot & \rightarrow \text{Ar}^\cdot + \text{X}^- & (2) \\
\text{Ar} + \text{Nu} & \rightarrow (\text{ArNu}) & (3) \\
(\text{ArNu})^\cdot + \text{ArX} & \rightarrow \text{ArNu} + (\text{ArX})^\cdot & (4) \\
\text{ArX} + \text{Nu} & \rightarrow \text{ArNu} + \text{X} & (5)
\end{align*}
\]

One of the most widely studied approaches to ring closure reactions is the S_RN1 substitution of aromatic compounds that bear an appropriate substituent ortho to the leaving group. This
method has been recently applied to the synthesis of indoles,\textsuperscript{13} isoquinolin-1(2\textit{H})-ones,\textsuperscript{14} 2\textit{H}-1,2-benzothiazine-1,1-dioxides,\textsuperscript{15} dihydrophenalenones,\textsuperscript{16} etc.

The development of tandem reactions for the efficient construction of complex molecules is an important goal in organic synthesis in terms of operational simplicity and efficiency. In 1985, Beugelmans and Ginsburg performed the photostimulated reaction of 2-(2-iodo-4,5-dimethoxyphenyl)acetate ion 1\textsuperscript{−} with alkyl methyl ketone anions 2 (R=Me, \textit{i}-Pr, \textit{t}-Bu) in NH\textsubscript{3}(l), followed by ring closure with NH\textsubscript{4}OAc in acetic acid as solvent. As a result, they obtained good yields of the 4-alkyl-1,3-dihydro-2\textit{H}-3-benzazepin-2-ones 4 (equation 6).\textsuperscript{17}

\[
\begin{align*}
\text{MeO} & \text{O} \text{Me} \text{O} \text{Me} \text{I} + -\text{CH}_2\text{COR} & \rightarrow & \text{MeO} \text{O} \text{Me} \text{R} \text{MeO} \text{O} \text{Me} \\
1\textsuperscript{−} & 2 & \rightarrow & 3 \\
R=\text{Me, } \textit{i}-\text{Pr, } \textit{t}-\text{Bu} & \\
& & & 4 (50-60\%) \\
\end{align*}
\]

In this report, the methodology is extended to synthesize novel 3-benzazepin-2-one derivatives through a sequence of \textit{S\textsubscript{RN}1}-condensation reactions from commercially available 2-(2-iodophenyl)acetic acid 5. Primary and secondary ketone enolate ions were tested and DMSO was used as alternative solvent because it is more versatile and easier to manipulate than NH\textsubscript{3}(l). The \textit{S\textsubscript{RN}1} step was studied and optimized in order to obtain new \textepsilon-oxo acids. The possibility of performing the two reactions in a \textit{one-pot} approach was also examined in order to gain rapid access to different of 3-benzazepin-2-ones.

\textbf{Results and Discussion}

The reaction of 5\textsuperscript{−} with the pinacolone enolate ion 2\textit{a} (4 equiv) was studied in NH\textsubscript{3}(l), the solvent of choice for the majority of aromatic \textit{S\textsubscript{RN}1} reactions since the H abstraction by radicals in this medium is a slow process.\textsuperscript{18} Under these conditions, the desired \textepsilon-oxo acid 3\textit{a} (80% yield) and the reduced substrate 6 (not quantified) were obtained (equation 7; Table 1, entry 1).

\[
\begin{align*}
\text{MeO} & \text{O} \text{I} + -\text{CH}_2\text{COBu-t} & \rightarrow & \text{MeO} \text{O} \text{Me} \text{R} \text{MeO} \text{O} \text{Me} \\
5\textsuperscript{−} & 2\textit{a} & \rightarrow & 3\textit{a} (80\%) + 6 + 1\textsuperscript{−} \\
\text{NH}_3(l) & \text{h}_\nu & \\
\end{align*}
\]
Table 1. Photostimulated reactions of anions from aliphatic ketones with 5<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Conditions</th>
<th>Products</th>
<th>Products (Yield%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-CH&lt;sub&gt;2&lt;/sub&gt;COBu-&lt;i&gt;t&lt;/i&gt;</td>
<td>60 min, NH&lt;sub&gt;3(l)&lt;/sub&gt;</td>
<td><img src="3a.png" alt="image" /></td>
<td>3a (80%)</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>60 min, NH&lt;sub&gt;3(l)&lt;/sub&gt;</td>
<td><img src="3b.png" alt="image" /></td>
<td>3b (0%)</td>
</tr>
<tr>
<td>3</td>
<td>2a</td>
<td>60 min, DMSO</td>
<td>3a + 6</td>
<td>3a (86%) + 6 (13%)</td>
</tr>
<tr>
<td>4</td>
<td>2b</td>
<td>60 min, DMSO</td>
<td>3b + 6</td>
<td>3b (55%) + 6 (45%)</td>
</tr>
<tr>
<td>5&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>60 min, DMSO, dark conditions</td>
<td>3b</td>
<td>3b (0%)</td>
</tr>
<tr>
<td>6</td>
<td>2b</td>
<td>60 min, DMSO, 30% m-DNB</td>
<td>3b</td>
<td>3b (19%)</td>
</tr>
<tr>
<td>7</td>
<td>t-CH&lt;sub&gt;2&lt;/sub&gt;COMe</td>
<td>120 min, DMSO</td>
<td><img src="3c.png" alt="image" /> + 6</td>
<td>3c (82%)&lt;sup&gt;e&lt;/sup&gt; + 6 (18%)</td>
</tr>
<tr>
<td>8</td>
<td>t-CH&lt;sub&gt;2&lt;/sub&gt;COEt</td>
<td>120 min, DMSO</td>
<td><img src="3d.png" alt="image" /> + 6</td>
<td>3d (24%) + 6 (41%)</td>
</tr>
<tr>
<td>9</td>
<td>t-CH&lt;sub&gt;2&lt;/sub&gt;COBu-&lt;i&gt;i&lt;/i&gt;</td>
<td>120 min, DMSO</td>
<td><img src="3e.png" alt="image" /> + 6</td>
<td>3e (57%) + 6 (25%)</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>120 min, DMSO</td>
<td><img src="3f.png" alt="image" /> + 6</td>
<td>3f (22%) + 6 (65%)</td>
</tr>
<tr>
<td>11&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td>120 min, NH&lt;sub&gt;3(l)&lt;/sub&gt;</td>
<td><img src="3f.png" alt="image" /> + 6</td>
<td>3f (13%) + 6 (51%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>The reactions were performed in 8 mL of DMSO (or in 60 mL of NH<sub>3(l)</sub>), with 1 mmol of substrate 5, 4 mmol of the ketone and 5.5 mmol of t-BuOK. Irradiation was conducted in a photochemical reactor equipped with two HPI-T 400 W lamps (cooled with air and water).

<sup>b</sup>Yields were determined by <sup>1</sup>H NMR (internal standard method).<sup>c</sup>The reduced substrate 6 was the main product, detected but not quantified.<sup>d</sup>The substrate was recovered in 83%. <sup>e</sup>59% isolated yield.<sup>f</sup>The substrate was recovered in 18%.
It is proposed that rigid polycyclic moieties such as adamantyl could improve the biological activity of compounds by increasing their lipophilic property. In addition, many compounds containing this polycyclic group have shown biological activity. In the photostimulated reaction (60 min) of 5 with the anion derived from 1-adamantylmethylketone 2b, no arylation product was found, and only the corresponding reduced compound 6 was obtained (Table 1, entry 2). This lack of substitution could be attributed to the low solubility of anion 2b in NH₃(l). Due to this limitation, the solvent was changed to DMSO, another suitable solvent for S_{RN1} reactions, which is more versatile and easier to be manipulated than ammonia. In this medium, the irradiated reaction of 5 (1 equiv) with 2a (4 equiv) afforded 86% of 3a accompanied with only 13% of 6 (Table 1, entry 3).

On the basis of the similar substitution outcome obtained with anion 2a in both solvents, the reaction of 5 with 2b was carried out in DMSO, obtaining 55% of 3b with 45% of 6 (Table 1, entry 4). This reaction did not occur in the dark (entry 5) and partial inhibition was observed when irradiated in the presence of 1,3-dinitrobenzene, a well-known inhibitor of S_{RN1} reactions (entry 6). These results indicate that the substitution reaction proceeds by the S_{RN1} mechanism (Scheme 1).

The initiation step being the photoinduced ET yielding radical dianion 5⁻. Fragmentation of the C-I bond of 5⁻ gave the distonic radical anion 7⁻ and I⁻ ion. The intermediate radical anion 7⁻ coupled with ketone enolate anion 2 to yield the radical dianion 8⁻. An ET from 8⁻ to 5⁻ afforded the ε-oxo acid anion intermediate 9⁻ and radical dianion 5⁻, which propagates the reaction. Intermediate 9⁻ gave product 3 upon acidification of the reaction medium during the work-up (Scheme 1). A reaction that could compete with the coupling reaction of radical anion 7⁻ is its reduction by hydrogen abstraction to yield anion 6⁻ that, upon acidification, affords the reduced substrate 6.

Other ketone enolate ions were tested to extend the scope of the system. In the photostimulated reaction of 5 with acetonate anion 2c in DMSO the ε-oxo acid 3c was formed in 82% yield (Table 1, entry 7). As result of the good yields obtained with primary enolate ion derivatives, the reactivity and regiochemistry of phenyl radical anion 7⁻ toward primary and secondary enolate ions was determined.

With unsymmetrical dialkyl ketones, isomeric enolate ions can be formed. The distribution of the two possible arylated products is mainly determined by the equilibrium concentration of the two possible enolate ions and the selectivity of the attacking radical. For example, the reaction of halobenzenes with 2-butanone and i-propylmethyl ketone enolate ions has been shown to give the two possible substitution products, but with different ratios. Similar results have been described in the reaction of 2-chloroquinoline and i-propylmethyl ketone enolate ion.

2-Butanone can form isomeric enolate ions 2d and 2d'. However, 7⁻ reacts exclusively with 2d to yield the ε-oxo acid 3d in a 24% yield; no traces of product 10 being found (Scheme 2; Table 1, entry 8).
Scheme 1. Mechanism proposed for S_{RN1} reaction of 5^{-} with alkyl ketone enolate ions.

Scheme 2. Reaction of 7^{-} with 2d anion.

The same substitution regiospecificity was found in the reaction of 7^{-} with methyl isobutyl anion 2e. In this case, the substitution product 3e was formed also exclusively in 57% yield and the reduced substrate 6 in 25% yield (Scheme 3; Table 1, entry 9). These results indicate that radical anion 7^{-} exhibits a high degree of selectivity in its coupling reaction with enolate ions.

Scheme 3. Reaction of 7^{-} with 2e anion.
The decrease of substitution product and the increment of reduced substrate 6 in the experiments with 2e and 2d, (Table 1, entries 9 and 8), could be ascribed to the presence of β hydrogen in these enolate ions.\(^{23}\) In the presence of these ions, the radical anion 7\(^{-}\) could follow two reactions: coupling with anion 2 to finally give the expected ε-oxo acid 3e-d or β hydrogen abstraction (Scheme 4). When β hydrogen abstraction occurs, the conjugated radical anion 2\(^{-}\) is formed. This intermediate finally affords the α-β unsaturated ketone by an ET reaction.\(^{21b,23}\) Although the ε-oxo acid is not formed, this reaction would serve as a propagation step in the radical-chain mechanism.

\[
\begin{align*}
\text{Coupling reaction} & \quad 3e \ (57\%) \ R=R^1=\text{Me} \\
\beta \text{ hydrogen abstraction} & \quad 3d \ (24\%) \ R=R^1=\text{H} \\
\end{align*}
\]

**Scheme 4.** Coupling reaction vs β hydrogen abstraction.

In order to determine the reactivity of 7\(^{-}\) toward secondary enolate ions, the reaction of 5\(^{-}\) with the cyclohexanone anion 2f was studied in DMSO. This anion could not form isomeric primary enolate. In this reaction the desired ε-oxo acid 3f was formed in 22% yield (Table 1, entry 10). When the reaction was performed in NH\(_3\)\(_2\)OH under irradiation (120 min), 3f was obtained in 13% yield together with 18% yield of substrate 5 and 51% of 6 (Table 1, entry 11).

In experiments not tabulated but similar in design to those of Table 1, efforts were made to obtain ε-oxo acid with other secondary enolates. Unfortunately the enolates of cyclopentanone 11, bicycle[2.2.1]heptan-2-one 12 and 1,7,7-trimethylbicycle[2.2.1]heptan-2-one 13 failed to couple with 7\(^{-}\) and only substrate 5 and the reduced product 6 were found. In the reactions of 5\(^{-}\) with 11, 12 and 13, the products and yields obtained were: 5 (8%), 6 (81%), 5 (20%) and 6 (66%), 5 (61%) and 6 (29%) respectively. The low reactivity of 5\(^{-}\) is probably due to the fact that intermediate radical anion 7\(^{-}\) presents a flexible and negatively charged chain that slow down the coupling reaction with these cyclic nucleophiles (equation 8, Scheme 5) and it favors the reduction reaction by hydrogen abstraction (equation 9, Scheme 5).

This idea is based on the fact that the analog substrate 2-iodobenzoate anion, which lacks the methylene group, reacts with cyclic enolate ions in very good yields.\(^{24}\)

In order to determine the relative S\(_{\text{RN1}}\) reactivity of 5\(^{-}\) compared to other haloaromatic compounds, a competitive reaction was conducted employing PhI and 5\(^{-}\). Irradiation in DMSO for 5 min of an equimolecular mixture of 5\(^{-}\) and PhI in the presence of 2a affords 3a and 3,3-dimethyl-1-phenylbutan-2-one 14 in 30% and 41% yields, respectively (equation 10). This
experiment shows that 5− is less reactive than PhI with a ratio of 0.73:1.00, toward the S_{RN1} reaction with 2a.

\[
\begin{align*}
\text{Nu}^- = & \text{Cyclohexanone, Pinacolone, Acetone} \\
& \text{5}^- + \text{1} + \text{2a} \xrightarrow{\text{DMSO, hv}} \text{3a (30%) + 14 (41%)}
\end{align*}
\]

**Scheme 5.** Competitive reactions of 7−. Coupling vs hydrogen abstraction for secondary enolate ions.

Previously, it has been determined that the relative reactivity of carbanions of aliphatic ketones toward the Ph· radical in DMSO follows the order of: cyclohexanone (0.51), pinacolone (1.00) and acetone (1.09).\(^{25}\) Bearing in mind that the reactivity of acetonate ion is similar to that of pinacolone enolate ion, the reactivity of 5− could be included in the reactivity sequence of different haloarenes toward acetonate anion, this being:\(^{26}\) 2-haloquinoline > 2-halopyridine > PhI > 5−. This sequence demonstrates that the negative charge influences not only the selectivity of the coupling reaction, but also reduces the reactivity of the distonic radical anion 7− toward carbanions.

With the aim of obtaining the 3-benzazepin-2-ones, the possibility of synthesizing the target compounds without the isolation of ε-oxo acid was studied.

The photostimulated reaction of 5− and 2a in DMSO for 60 min was performed. During the work-up, the reaction mixture was extracted with EtOAc following the procedure indicated in the experimental section. Ammonium acetate in glacial acetic acid were added to the crude S_{RN1}
product mixture of acid 3a and 6, and the mixture was heated at reflux for 120 min. The desired product 4-tert-butyl-1,3-dihydro-2H-3-benzazepin-2-one 4a was obtained in 69% (by 1H NMR) and isolated in 59% yield respectively (equation 11; Table 2, entry 1).

Following the procedure previously described, the consecutive S\textsubscript{RN}1-condensation reactions of 5\textsuperscript{-} with different alkyl enolate ions 2b-e afforded, through a one-pot procedure, the corresponding novel 3-benzazepin-2-ones 4b-e with 18-66% global yields (Table 2, entries 2-5). 3-Alkylbenzazepin-2-ones were obtained as a white crystalline solid and their 1H NMR spectrum exhibited a singlet for the olefin proton at 6-6.5 ppm that allowed its quantification.

Furthermore, in the photoinitiated reaction of anion 2f in DMSO as solvent (120 min) and subsequent condensation, a new tricyclic 3,4,5,7-tetrahydro-1H-dibenzo[b,d]azepin-6(2H)-one 4f was formed in 18% global yield (Table 2, entry 6).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>ProductYield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a (69%)\textsuperscript{c}</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4b (22%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4c (66%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Synthesis of 3-benzazepin-2-ones 4a-f by S\textsubscript{RN}1-condensation consecutive sequence reactions through a one-pot procedure\textsuperscript{a}

\textsuperscript{a} Process conditions: 5\textsuperscript{-} + 2a \xrightarrow{DMSO, \text{hv}} 3a \xrightarrow{NH\textsubscript{2}OAc, HOAc, 120 min reflux} 4a

\textsuperscript{b} isolated yield

\textsuperscript{c} by 1H NMR
Table 2. (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Product Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td><img src="image1.png" alt="Image" /></td>
<td>4d (18%)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image2.png" alt="Image" /></td>
<td>4e (49%)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image3.png" alt="Image" /></td>
<td>4f (18%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>The reactions were performed in 4mL of glacial acetic acid, with 2 g of ammonium acetate for 1 mmol of 5. The crude product was refluxed during 120 min. <sup>b</sup>Global yields were determined by <sup>1</sup>H NMR (internal standard method). <sup>c</sup>59% isolated yield.

Conclusions

In this work we present a simple and readily available method for the synthesis of ε-oxo acids and six novel 3-benzazepin-2-ones, using commercially available 2-(2-iodophenyl)acetic acid 5 and alkyl ketone as starting materials. The synthetic strategy involves a photostimulated <sup>SN1</sup> substitution reaction of 5<sup>•</sup> with different ketone enolate ions, followed by a condensation reaction. The use of DMSO as solvent, instead of NH<sub>3</sub>(l), makes this approach more versatile, practical and simple. The <sup>SN1</sup> mechanism accounts for the substitution reactions; the ε-oxo acids being obtained in very good yields for alkyl methyl ketones (55-86%). The intermediate radical anion 7<sup>•</sup> exhibits a high degree of selectivity toward primary enolate ions. For this reason the enolates ions from 2-butaneone and isobutyl methyl ketone exclusively afford 3d and 3e ε-oxo acids. Moreover, secondary enolates coupled with 7<sup>•</sup> in low yields (22%). Considering the availability of the starting materials, and the simplicity and mild conditions of the procedure, we have demonstrated that this can be a general methodology for the synthesis of this family of compounds.
Experimental Section

General. $^1$H NMR (400.16 MHz) and $^{13}$C NMR (100.62 MHz) were conducted in Cl$_3$CD as a solvent otherwise indicated, and referenced with residual solvent signal. Coupling constants ($J$) are given in Hertz. Quantification by $^1$H NMR was performed by adding a standard to the crude in Cl$_3$CD as solvent. Data are reported as follows: chemical shift, integration and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sx = sextet, h = heptet, m = multiplet and br = broad), coupling constant in Hz. Gas chromatographic (GC) analyses were performed on an instrument with a flame ionization detector equipped with a VF-5ms column (30 m x 0.25 mm x 0.25 μm). Gas chromatographic-mass spectrometer analyses were carried out on an instrument equipped with a quadrupole detector and a VF-5ms column (30 m x 0.25 mm x 0.25 μm). High Resolution mass spectra were done in a MS/MS instrument in pure products.

Materials. Radial thin layer chromatography purifications, 2 mm plates (silica gel 60 PF 254) were used. DMSO was dried and stored over molecular sieves (4 Å). Acetone, pinacolone, cyclohexenone, 2-butanone and 4-methylpentan-2-one were distilled and stored over molecular sieves (4Å), 2-(2-iodophenyl)acetic acid, 1-adamantyl methyl ketone, bicycle[2.2.1]heptan-2-one, 1,7,7-trimethylbicycle[2.2.1]heptan-2-one, t-BuOK, NH$_4$OAc and NH$_4$NO$_3$ were commercially available and they were used just as they were received from the supplier. In all purifications analytical grade, solvents were distilled before use.

Representative procedure for photostimulated reactions

Preparation of ε-oxo acid (3a) in DMSO. In a previously flame-dried 25 mL Schlenk tube equipped with a magnetic stirrer were added 8 mL of DMSO under nitrogen. The solvent was degassed with vacuum and then t-BuOK (5.5 equiv, 616.0 mg) and the conjugated acids of the nucleophiles (4 equiv. of pinacolone, 500 μL) were added. After 10 min, solid 2-(2-iodophenyl)acetic acid 5 (1.0 equiv, 262.0 mg) was added. The reactions were irradiated using two HPI-T 400 W lamps ($\lambda_{max}$: 530 and 590 nm) for the times indicated in Table 1. After irradiation, the reactions were quenched by adding ammonium nitrate and water in excess. The aqueous phase was extracted twice with ethyl acetate (50 mL) and the aqueous phase was then acidified with HNO$_3$. The aqueous phase was re-extracted with ethyl acetate (3 x 50 mL). Afterwards, the last organic extract was dried over anhydrous Na$_2$SO$_4$, and then filtered, and the solvent was removed under reduced pressure to leave the crude products. The products were separated and isolated by radial thin-layer chromatography on silica gel. In other similar experiments the products were quantified by $^1$H NMR by using the internal standard method.

Competition reaction of pinacolone enolate ion with (5) and PhI. A mixture of PhI (204.0 mg, 1 mmol) and 5 (262.0 mg, 1 mmol) was added under irradiation to the enolate ion solution prepared from 400.6 mg (4 mmol) of pinacolone and 5.5 mmol of t-BuOK (616.0 mg) in 8 mL of DMSO. After a 5 min of irradiation, the mixture was quenched with ammonium nitrate and water in excess. The aqueous phase was acidified with HNO$_3$ and extracted with ethyl acetate (3
× 20 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The analysis by ¹H NMR and CG showed partial consumption of 5 and PhI, giving 3a and 3,3-dimethyl-1-phenylbutan-2-one 14 and a ratio of 0.73:1.00.

**Representative procedure for photostimulated reactions: preparation of ε-oxo acid (3a) in liquid ammonia**

The following procedure is representative of all these reactions. NH₃(l) (60 mL), previously dried over Na metal, was distilled into a 100 mL three-necked, round-bottomed flask equipped with a cold finger condenser and a magnetic stirrer under a nitrogen atmosphere. The base i-BuOK (5.5 equiv, 616.0 mg) was added and then pinacolone (4.0 equiv, 500 µL). After 10 min, 5 (1.0 equiv, 262.2 mg) was added to the NH₃(l) and the solution was irradiated for 60 min. The reaction was quenched with an excess of ammonium nitrate and the NH₃(l) was allowed to evaporate. Water was added to the residue and the mixture was extracted with ethyl acetate (3 × 50 mL). The aqueous phase was carried out to pH near 1 with HNO₃ and extracted with ethyl acetate (3 × 50 mL). The last organic extract was dried over anhydrous Na₂SO₄ then filtered, and the solvent was removed to leave the crude products. The products were separated and isolated by radial thin-layer chromatography on silica gel. In other similar experiments the products were quantified by ¹H NMR by using the internal standard method.

**2-[2-(3,3-Dimethyl-2-oxobutyl)phenyl]acetic acid (3a).** Slightly yellow liquid purified by radial thin layer chromatography using petroleum/diethyl ether (80:20 → 0:100) as solvent. ¹H NMR (CDCl₃) δ 1.24 (9H, s), 3.55 (2H, s), 3.94 (2H, s), 7.05 (1H, m), 7.27 (3H, m). ¹³C NMR (CDCl₃) δ 26.5, 39.1, 41.1, 44.6, 127.4, 127.6, 130.8, 130.9, 133.0, 134.0, 175.6, 213.3. ¹H-¹H COSY NMR (CDCl₃) δ_H/δ_H 7.05/7.27. ¹H-¹³C HSQC NMR (CDCl₃) δ_H/δ_C 1.24/26.5, 3.55/39.1, 3.94/41.1, 7.05/130.9, 7.27/127.4, 7.27/127.6, 7.27/130.8. GC-MS (m/z) 234 (7, M⁺), 150 (14), 149 (12), 132 (55), 121 (12), 119 (9), 105 (27), 104 (38), 103 (12), 93 (10), 91 (18), 85 (24), 78 (11), 77 (20), 58 (10), 57 (100), 41 (43). ESI-HRMS Anal. Calcd for C₁₄H₁₉O₃⁺ (M+ H⁺) 235.1329, found 235.1356.

**{2-[2-(1-Adamantyl)-2-oxoethyl]phenyl]acetic acid (3b).** The product was purified by radial thin-layer chromatography on silica gel eluting with petroleum ether/diethyl ether (80:20 → 50:50): white crystals; mp 112.0-113.0 °C. ¹H NMR (CDCl₃) δ 1.75 (6H, q), 1.90 (6H, d), 2.08 (3H, s), 3.53 (2H, s), 3.89 (2H, s), 7.04 (1H, m), 7.25 (3H, m). ¹³C NMR (CDCl₃) δ 27.9, 36.5, 38.3, 39.0, 40.7, 46.8, 127.4, 127.7, 130.7, 131.0, 132.8, 134.0, 176.4, 213.1. ¹H-¹H COSY NMR (CDCl₃) δ_H/δ_H 1.74/2.08, 1.91/2.08, 7.04/7.25. ¹H-¹³C HSQC NMR (CDCl₃) δ_H/δ_C 1.75/36.5, 1.90/39.0, 2.08/27.9, 3.53/39.0, 3.89/40.7, 7.04/131.0, 7.25/127.4, 7.25/127.7, 7.25/130.7. ¹H-¹³C HMBC NMR (CDCl₃) δ_H/δ_C 1.75/27.9, 1.75/36.5, 1.75/38.3, 1.90/27.9, 1.90/36.5, 1.90/38.3, 1.90/46.8, 1.90/213.1, 2.08/27.9, 2.08/38.3, 2.08/46.8, 3.53/130.7, 3.53/132.8, 3.53/176.4, 3.89/130.7, 3.89/132.8, 3.89/134.0, 3.89/213.1, 7.04/40.7, 7.04/127.4, 7.04/132.8, 7.04/134.0, 7.25/39.0, 7.25/127.7, 7.25/130.7, 7.25/132.8, 7.25/134.0. GC-MS (m/z)
267 (1), 165 (2), 136 (13), 135 (100), 107 (10), 93 (17), 91 (19), 79 (19), 77 (9). ESI-HRMS Anal. Calcd for C_{20}H_{24}O_3Na^+(M+Na^+) 335.1618, found 335.1628.

2-[2-(2-Oxopropyl)phenyl]acetic acid (3e). Slightly yellow liquid purified by radial thin layer chromatography using petroleum ether/diethyl ether mixture (70:30→50:50) as solvent. ^1H NMR (CDCl$_3$) δ 2.16 (3H, s), 3.61 (2H, s), 3.79 (2H, s), 7.16 (1H, s), 7.25 (3H, m), 8.87 (1H, s br). ^13C NMR (CDCl$_3$) δ 29.4, 38.7, 48.6, 127.7, 128.0, 131.0, 131.1, 132.6, 133.4, 176.8, 206.5. ^1H-^1H COSY NMR (CDCl$_3$) δ$_H$/δ$_H$ 2.16/3.79, 7.16/7.25. ^1H-^13C HSQC NMR (CDCl$_3$) δ$_H$/δ$_C$ 2.16/29.4, 3.61/38.7, 3.79/48.6, 7.16/131.1, 7.25/127.7, 7.25/128.0, 7.25/131.0. ^1H-^13C HMBC NMR (CDCl$_3$) δ$_H$/δ$_C$ 2.16/48.6, 2.16/206.5, 3.61/131.0, 3.61/131.1, 3.61/132.6, 3.61/133.4, 3.61/176.8, 3.79/131.0, 3.79/132.6, 3.79/133.4, 3.79/206.5, 7.16/48.6, 7.16/127.7, 7.16/132.6, 7.25/38.7, 7.25/128.0, 7.25/131.1, 7.25/132.6, 7.25/133.4. GC-MS (m/z) 192 (3, M$^+$), 132 (30), 121 (11), 105 (24), 104 (58), 103 (17), 93 (20), 91 (22), 78 (16), 77 (29), 51 (10), 43 (100).

2-[2-(2-Oxobutyl)phenyl]acetic acid (3d). Slightly yellow liquid purified by radial thin layer chromatography using petroleum ether/ethyl acetate mixture (80:20→50:50) as solvent. ^1H NMR (CDCl$_3$) δ 1.02 (3H, t), 2.55 (2H, q), 3.63 (2H, s), 3.78 (2H, s), 7.14 (1H, m), 7.21 (3H, m), 8.26 (1H, s br). ^13C NMR (CDCl$_3$) δ 7.7, 35.4, 38.8, 47.3, 127.6, 127.9, 131.0, 131.0, 132.6, 133.6, 176.6, 209.0. ^1H-^13C HSQC NMR (CDCl$_3$) δ$_H$/δ$_C$ 1.02/7.7, 2.55/35.4, 3.63/38.8, 3.78/47.3, 7.14/131.0, 7.21/127.6, 7.21/131.0, 7.21/127.9. ^1H-^13C HMBC NMR (CDCl$_3$) δ$_H$/δ$_C$ 1.02/35.4, 1.02/209.0, 2.55/7.7, 2.55/209.0, 3.63/131.0, 3.63/176.6, 3.78/131.0, 3.78/133.6, 7.14/127.6, 7.21/132.6. GC-MS (m/z) 206 (3, M$^+$), 132 (42), 105 (22), 104 (56), 103 (25), 93 (16), 91 (22), 78 (20), 77 (38), 57 (100), 43 (28).

2-[2-(4-Methyl-2-oxopentyl)phenyl]acetic acid (3e). Slightly yellow liquid purified by radial thin layer chromatography using petroleum ether/diethyl ether mixture (80:20→10:90) as solvent. ^1H NMR (CDCl$_3$) δ 0.89 (6H, d, J=6.7), 2.14 (1H, h, J=6.8), 2.36 (2H, d, J=7.0), 3.63 (2H, s), 3.77 (2H, s), 7.15 (1H, m), 7.26 (3H, m). ^13C NMR (CDCl$_3$) δ 22.5, 24.5, 38.7, 48.2, 51.3, 127.7, 128.0, 131.0, 131.1, 132.7, 133.4, 176.0, 208.2. ^1H-^1H COSY NMR (CDCl$_3$) δ$_H$/δ$_H$ 0.89/2.14, 2.14/2.36, 7.15/7.26. ^1H-^13C HSQC NMR (CDCl$_3$) δ$_H$/δ$_C$ 0.89/22.5, 2.14/24.5, 2.36/51.3, 3.63/38.7, 3.77/48.2, 7.15/131.1, 7.26/127.7, 7.26/128.0, 7.26/131.0. ^1H-^13C HMBC NMR (CDCl$_3$) δ$_H$/δ$_C$ 0.89/22.5, 0.89/24.5, 0.89/51.3, 2.14/22.5, 2.14/51.3, 2.36/22.5, 2.36/24.5, 2.36/208.2, 3.63/131.1, 3.63/132.7, 3.63/176.0, 3.77/131.0, 3.77/133.4, 3.77/208.2, 7.15/127.7, 7.15/132.7, 7.26/128.0, 7.26/131.0, 7.26/132.7, 7.26/133.4. GC-MS (m/z) 216 (14), 188 (11), 132 (13), 105 (12), 104 (25), 85 (100), 78 (8), 57 (96), 45 (9), 43 (8), 41 (27). ESI-HRMS Anal. Calcd for C_{16}H_{19}O_3$^+$ (M+H$^+$) 235.1329, found 235.1321.

2-(2-Oxocyclohexyl)phenyl]acetic acid (3f). The crude S_{RN1} reaction was used without further purification (difficult at the stage) for the synthesis of 3-ben佐azepinone 4f.

Representative procedure for one-pot synthesis of benzodiaze pinones

The crude S_{RN1} product mixture of acids 3 and 6 was used without purification. In a round-bottomed flask, the crude product of the S_{RN1} reaction (0.150 g) was added 2 g of NH$_4$OAc and 4 mL of glacial acetic acid. The crude was refluxed during 120 min. After cooling and adding K$_2$CO$_3$, the crude of the reaction was extracted with ethyl acetate (3 × 50 mL). The organic
extract was dried over anhydrous Na₂SO₄ then filtered, and the solvent was removed to leave the crude products.

4-tert-Butyl-1,3-dihydro-2H-3-benzazepin-2-one (4a). The benzazepinone 4a was purified by radial thin-layer chromatography on silica gel eluting with a petroleum ether/diethyl ether gradient (60:40–50:50) as white crystals and isolated in 59% yield, m.p.: 153-154 °C. ¹H NMR (CD₂COCD₂) δ1.28 (9H, s), 3.45 (2H, s), 6.42 (1H, s), 6.98 (1H, s), 7.27 (4H, m). ¹³C NMR (CD₂COCD₂) δ29.0, 36.1, 42.7, 111.6, 127.0, 127.7, 128.2, 132.8, 131.3, 134.4, 144.9, 170.3. ¹H-¹³C HSQC NMR (CD₂COCD₂) δH/δC 1.28/29.0, 3.45/42.7, 6.42/111.6, 7.27/127.0, 7.27/127.7, 7.27/128.2, 7.27/128.5.

GC m/z 215 (M⁺), 100, 200 (31), 186 (23), 172 (17), 170 (12), 158 (18), 157 (33), 156 (13), 155 (19), 142 (12), 132 (42), 131 (23), 130 (40), 129 (22), 128 (16), 116 (13), 115 (22), 103 (31), 102 (18), 85 (19), 84 (18), 78 (12), 77 (34), 57 (37), 51 (12). ESI-HRMS Anal. Calcd for C₁₄H₁₈NO⁺ (M+ H⁺) 216.1383, found 216.1373.

4-(1-Adamantyl)-1,3-dihydro-2H-3-benzazepin-2-one (4b). The benzazepinone 4b was purified by column chromatography on silica gel eluting with a petroleum ether/diethyl ether gradient (60:40–50:50) as white crystals, m.p. 220-221 °C. ¹H NMR (CD₂COCD₂) δ1.79 (6H, t), 1.97 (6H, d), 2.09 (3H, s), 3.35 (2H, s), 3.69 (1H, s), 7.28 (4H, m), 8.3 (1H, s br). ¹³C NMR (CD₂COCD₂) δ29.6, 37.3, 38.7, 41.4, 113.3, 127.6, 128.5, 128.7, 129.0, 133.0, 136.1, 147.8, 170.5. ¹H-¹³C HSQC NMR (CD₂COCD₂) δH/δC 1.79/37.3, 1.79/41.4, 1.97/29.6, 3.35/42.7, 6.39/111.5, 7.28/127.6, 7.28/128.5, 7.28/128.7, 7.28/129.0.

GC m/z 293 (M⁺, 100), 265 (13), 264 (45), 158 (16), 135 (77), 133 (11), 132 (65), 131 (21), 130 (38), 128 (12), 115 (13), 107 (13), 104 (12), 103 (11), 93 (22), 91 (18), 79 (25), 77 (23), 67 (15), 55 (12). ESI-HRMS Anal. Calcd for C₂₀H₂₄NO⁺ (M+ H⁺) 294.1852, found 294.1875.

4-Methyl-1,3-dihydro-2H-3-benzazepin-2-one (4c). The benzazepinone 4c was purified by recrystallization from diethyl ether as white crystals, m.p.: 181-182 °C. ¹H NMR (CD₂COCD₂) δ2.14 (3H, s), 3.43 (2H, s), 6.27 (1H, s), 7.24 (4H, m), 8.44 (1H, s br). ¹³C NMR (CD₂COCD₂) δ22.9, 44.1, 113.3, 127.7, 127.9, 128.4, 129.3, 131.9, 135.8, 136.2, 169.5. ¹H-¹³C HSQC NMR (CD₂COCD₂) δH/δC 2.14/22.9, 3.43/44.1, 6.27/113.3, 7.24/127.7, 7.24/127.9, 7.24/128.4, 7.24/129.3.

GC m/z 173 (M⁺, 100), 144 (47), 132 (42), 131 (45), 130 (78), 129 (26), 128 (19), 115 (32), 103 (12), 102 (10), 77 (18), 72 (20), 63 (11), 51 (12), 44 (12), 42 (28). ESI-HRMS Anal. Calcd for C₁₁H₁₂NO⁺ (M+ H⁺) 174.0913, found 174.0939.
4-Ethyl-1,3-dihydro-2H-3-benzazepin-2-one (4d). The benzazepinone 4d was purified by radial thin-layer chromatography on silica gel eluting with a petroleum ether/diethyl ether gradient (50:50→30:70) as white crystals, m.p.: 185-186 °C. 1H NMR (CDCl3) δ 1.22 (3H, t), 2.35 (2H, q), 3.48 (2H, s), 6.24 (1H, s), 7.19 (1H, m), 7.26 (3H, m), 7.71 (1H, s br). 13C NMR (CDCl3) δ 12.8, 29.8, 43.1, 112.5, 127.0, 127.4, 128.0, 128.7, 130.6, 134.6, 139.0, 170.2. 1H-13C HSQC NMR (CDCl3) δH/δC 1.22/12.8, 2.35/29.8, 3.48/43.1, 6.24/112.5, 7.19/127.4, 7.26/127.0, 7.26/128.0, 7.26/128.7. 1H-13C HMBC NMR (CDCl3) δH/δC 1.22/29.8, 1.22/130.6, 2.35/128.0, 2.35/112.5, 2.35/139.0, 3.48/128.7, 3.48/130.6, 3.48/134.6, 3.48/170.2, 6.24/29.8, 6.24/127.4, 6.24/130.6, 7.19/128.7, 7.26/127.0. GC-MS (m/z) 188 (13), 187 (M+, 100), 158 (40), 144 (34), 143 (52), 142 (11), 141 (12), 132 (60), 131 (35), 130 (40), 129 (63), 128 (20), 116 (12), 115 (28), 104 (13), 103 (25), 102 (18), 89 (11), 78 (14), 77 (38), 76 (12), 65 (17), 63 (16), 56 (35), 51 (20).


4-Isopropyl-1,3-dihydro-2H-3-benzazepin-2-one (4e). The benzazepinone 4e was purified by column chromatography on silica gel eluting with a petroleum ether/diethyl ether gradient (80:20→0:100) as white crystals, m.p.: 109-110 °C. 1H NMR (CDCl3) δ 0.96 (6H, d, J = 6.4), 1.87 (1H, h, J = 6.9), 2.18 (2H, d, J = 7.4), 3.48 (2H, s), 6.21 (1H, s), 7.18 (1H, m), 7.26 (3H, m), 7.89 (1H, s br). 13C NMR (CDCl3) δ 22.2, 27.1, 43.1, 46.3, 114.7, 127.0, 127.2, 127.9, 128.6, 130.6, 134.6, 136.6, 170.2. 1H-1H COSY NMR (CDCl3) δH/δH 0.96/1.87, 1.87/2.18, 7.18/7.26. 1H-13C HSQC NMR (CDCl3) δH/δC 0.96/22.2, 1.87/27.1, 2.18/46.3, 3.48/43.1, 6.21/114.7, 7.18/127.2, 7.26/127.0, 7.26/127.9, 7.26/128.6. 1H-13C HMBC NMR (CDCl3) δH/δC 0.96/22.2, 0.96/27.1, 0.96/46.3, 1.87/22.2, 2.18/22.2, 2.18/27.1, 2.18/114.7, 2.18/136.6, 3.48/128.6, 3.48/130.6, 3.48/134.6, 3.48/170.2, 6.21/46.3, 6.21/127.2, 6.21/130.6, 6.21/136.6, 7.18/127.9, 7.26/127.0. GC-MS (m/z) 216 (16), 215 (M+, 100), 200 (16), 186 (11), 173 (37), 172 (22), 145 (29), 144 (74), 143 (33), 132 (51), 131 (29), 130 (63), 129 (36), 128 (25), 127 (18), 117 (13), 116 (15), 115 (32), 104 (11), 103 (19), 102 (14), 84 (14), 77 (24), 51 (10), 43 (11), 42 (10), 41 (16).

ESI-HRMS Anal. Calcd for C14H17ONa+ (M+ Na+) 238.1202, found 238.1226.

1,2,3,4,5,7-Hexahydro-6H-dibenzo[b,d]azepin-6-one (4f). The benzazepinone 4f was purified by radial thin-layer chromatography on silica gel eluting with a petroleum ether/diethyl ether gradient (50:50→0:100) as white crystals, mp 214-215 °C. 1H NMR (CDCl3) δ 1.80 (4H, s br), 2.31 (4H, m), 3.41 (2H, s br), 7.26 (3H, m), 7.36 (1H, m), 7.78 (1H, s br). 13C NMR (CDCl3) δ 22.6, 22.7, 29.2, 30.1, 42.8, 122.1, 125.1, 127.0, 127.9, 128.1, 131.2, 132.5, 138.3, 171.3. 1H-13C HSQC NMR (CDCl3) δH/δC 1.80/22.6, 1.80/22.7, 2.31/30.1, 2.31/29.2, 3.41/42.8, 7.26/127.0, 7.26/127.9, 7.26/128.1, 7.36/125.1. GC-MS (m/z) 214 (16), 213 (M+, 100), 185 (14), 184 (33), 170 (20), 169 (19), 168 (17), 167 (13), 157 (32), 156 (66), 145 (20), 144 (13), 143 (17), 142 (28), 141 (34), 130 (11), 129 (18), 128 (23), 127 (15), 117 (16), 116 (16), 115 (51), 91 (12), 89 (13), 78 (10), 77 (19), 65 (12), 63 (12), 51 (11), 41 (16). ESI-HRMS Anal. Calcd for C14H16NO+ (M+ H+) 214.1226, found 214.1237.
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References and Notes

27. Exhibited spectral data identical to those reported in reference 5.