Synthesis of ε-oxo acids by photostimulated reactions of 2-(2-iodophenyl)acetate ion with carbanions by the $S_{RN}1$ 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 $S_{RN}1$ substitution reaction in DMSO as solvent under photoinitiation, using ketone enolate ions as nucleophiles to obtain ε-oxo acids, followed by a condensation reaction of ε-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, ε-oxo acids, $S_{RN}1$ reactions, ketone enolate ions, electron transfer, photochemistry

Introduction

The γ-, δ-, and ε-oxo acids constitute valuable building blocks for the asymmetric synthesis of several carbo- and heterocycles including 4,4-disubstituted-1-naphthalenones,[1] pyrrolidines,[2] piperidones,[3] azepines[4] and 3-benzazepines.[4] However, a few methods with modest yields are available for their preparation. Recently, ε-oxo acids were synthesized from the diacid *o*-phenylenediacetic acid with organolithium (RLi, R = Me, Et, *n*-Bu, Ph) in regular to good yields (35-55%).[5] In this case, the selective formation of ε-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.[6] For

example, benzazepinones are ubiquitous structural units found in a large array of natural products[7a] and pharmaceuticals, with a broad spectrum of biological activity for the treatment of cardiovascular diseases,[7b] tumors,[7c] 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[8] or $Au(PPh_3)Cl$ /$AgSbF_6$-catalyzed[9] reactions with high regioselectivity and moderate to good yields.

The unimolecular radical nucleophilic substitution, or $S_{RN}1$ 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.[10] These anions react with aromatic halides under photostimulation in liquid ammonia ($NH_{3(l)}$) 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.[11,12]

The $S_{RN}1$ 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 $NH_{3(l)}$ or from a cathode) and inorganic salts (Fe^{2+}, SmI_2) 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.

Initiation Step

$$ArX + \text{Electron Donor} \longrightarrow (ArX)^{\bullet -} \quad (1)$$

Propagation Steps

$$(ArX)^{\bullet -} \longrightarrow Ar^{\bullet} + X^{-} \quad (2)$$

$$Ar^{\bullet} + Nu^{-} \longrightarrow (ArNu^{\bullet -}) \quad (3)$$

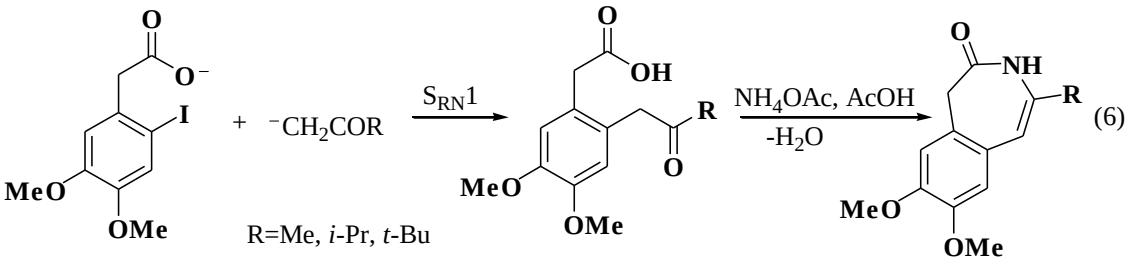
$$(ArNu)^{\bullet -} + ArX \longrightarrow ArNu + (ArX^{\bullet -}) \quad (4)$$

$$ArX + Nu^{-} \longrightarrow ArNu + {}^{-}X \quad (5)$$

One of the most widely studied approaches to ring closure reactions is the $S_{RN}1$ substitution of aromatic compounds that bear an appropriate substituent *ortho* to the leaving group.[12] This

method has been recently applied to the synthesis of indoles,[13] isoquinolin-1(2*H*)-ones,[14] 2*H*-1,2-benzothiazine-1,1-dioxides,[15] dihydrophenalenes,[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**$^-$ with alkyl methyl ketone anions **2** (R=Me, *i*-Pr, *t*-Bu) in $NH_{3(l)}$, followed by ring closure with NH_4OAc in acetic acid as solvent. As a result, they obtained good yields of the 4-alkyl-1,3-dihydro-2*H*-3-benzazepin-2-ones **4** (equation 6).[17]

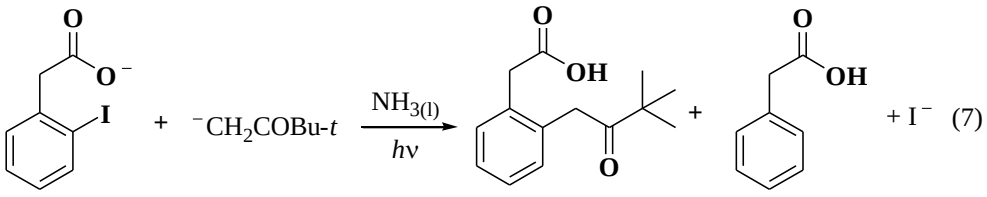


1$^-$ **2** **3** **4** (50-60%)

In this report, the methodology is extended to synthesize novel 3-benzazepin-2-one derivatives through a sequence of $S_{RN}1$-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 $NH_{3(l)}$. The $S_{RN}1$ step was studied and optimized in order to obtain new ε-oxo acids. The possibility of performing the two reactions in a *one-pot* approach was also examined in order to gain rapid access to different of 3-benzazepin-2-ones.

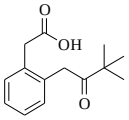
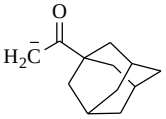
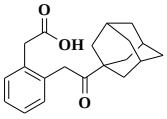
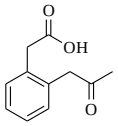
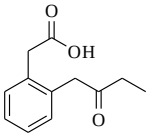
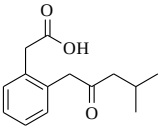
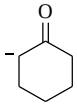
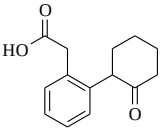
Results and Discussion

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



5$^-$ **2a** **3a** (80%) **6**

Table 1. Photostimulated reactions of anions from aliphatic ketones with $\mathbf{5}^{-}$ [a]

Entry	Nucleophile	Conditions	Products	Products (Yield%)[b]
1	$^{-}CH_2COBu$-*t* **2a**	60 min, $NH_{3(l)}$	 **3a**	**3a** (80%)
2[c]	 **2b**	60 min, $NH_{3(l)}$	 **3b**	**3b** (0%)
3	**2a**	60 min, DMSO	**3a + 6**	**3a** (86%) + **6** (13%)
4	**2b**	60 min, DMSO	**3b + 6**	**3b** (55%) + **6** (45%)
5[d]	**2b**	60 min, DMSO, dark conditions	**3b**	**3b** (0%)
6	**2b**	60 min, DMSO, 30% *m*-DNB	**3b**	**3b** (19%)
7	$^{-}CH_2COMe$ **2c**	120 min, DMSO	 **3c + 6**	**3c** (82%)[e] + **6** (18%)
8	$^{-}CH_2COEt$ **2d**	120 min, DMSO	 **3d + 6**	**3d** (24%) + **6** (41%)
9	$^{-}CH_2COBu$-*i* **2e**	120 min, DMSO	 **3e + 6**	**3e** (57%) + **6** (25%)
10	 **2f**	120 min, DMSO	 **3f + 6**	**3f** (22%) + **6** (65%)
11[f]	**2f**	120 min, $NH_{3(l)}$	**3f + 6**	**3f** (13%) + **6** (51%)

[a]The reactions were performed in 8 mL of DMSO (or in 60 mL of $NH_{3(l)}$), 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). [b]Yields were determined by ^{1}H NMR (internal standard method). [c]The reduced substrate **6** was the main product, detected but not quantified. [d]The substrate was recovered in 83%. [e]59% isolated yield. [f]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.[19] In the photostimulated reaction (60 min) of $\mathbf{5}^-$ 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 $NH_{3(l)}$.[20] Due to this limitation, the solvent was change to DMSO, another suitable solvent for $S_{RN}1$ reactions, which is more versatile and easier to be manipulated than ammonia. In this medium, the irradiated reaction of $\mathbf{5}^-$ (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 $\mathbf{5}^-$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 $S_{RN}1$ reactions[11a] (entry 6). These results indicate that the substitution reaction proceeds by the $S_{RN}1$ mechanism (Scheme 1).

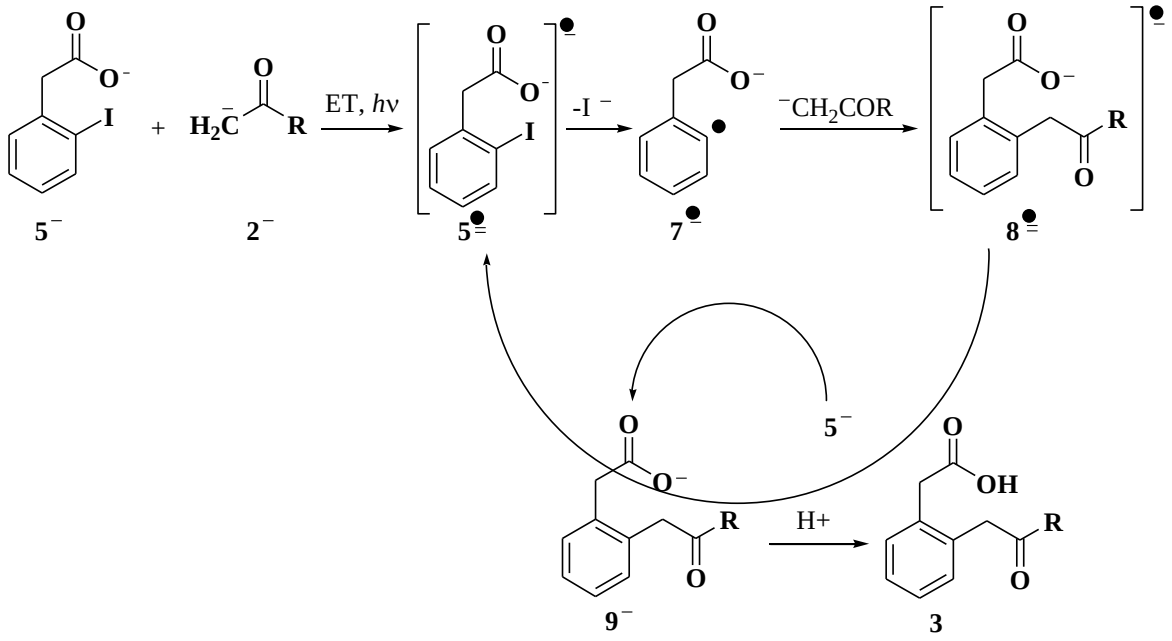
The initiation step being the photoinduced ET yielding radical dianion $\mathbf{5}^{\bullet\,=}$. Fragmentation of the C-I bond of $\mathbf{5}^{\bullet\,=}$ gave the distonic radical anion $\mathbf{7}^{\bullet\,-}$ and I^- ion. The intermediate radical anion $\mathbf{7}^{\bullet\,-}$ coupled with ketone enolate anion **2** to yield the radical dianion $\mathbf{8}^{\bullet\,=}$. An ET from $\mathbf{8}^{\bullet\,=}$ to $\mathbf{5}^-$ afforded the ε-oxo acid anion intermediate $\mathbf{9}^-$ and radical dianion $\mathbf{5}^{\bullet\,=}$, which propagates the reaction. Intermediate $\mathbf{9}^-$ 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 $\mathbf{7}^{\bullet\,-}$ is its reduction by hydrogen abstraction to yield anion $\mathbf{6}^-$ 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 $\mathbf{5}^-$ with acetonate anion **2c** in DMSO the ε-oxo acid **3c** was formed in 82% yield (Table 1, entry 7).

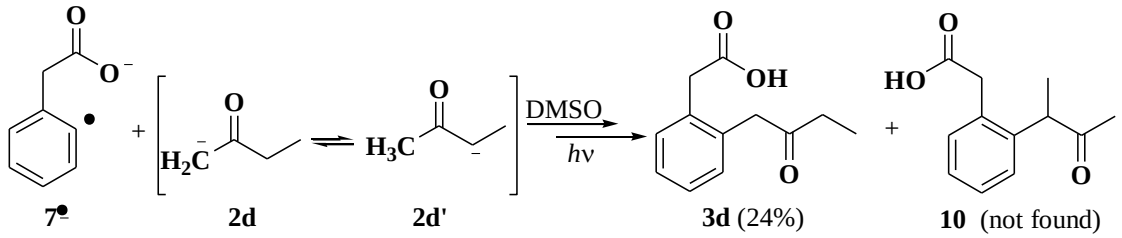
As result of the good yields obtained with primary enolate ion derivatives, the reactivity and regiochemistry of phenyl radical anion $\mathbf{7}^{\bullet\,-}$ toward primary and secondary enolate ions was determined.

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.[21] Similar results have been described in the reaction of 2-chloroquinoline and *i*-propylmethyl ketone enolate ion.[22]

2-Butanone can form isomeric enolate ions **2d** and **2d′**. However, $\mathbf{7}^{\bullet\,-}$ 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).

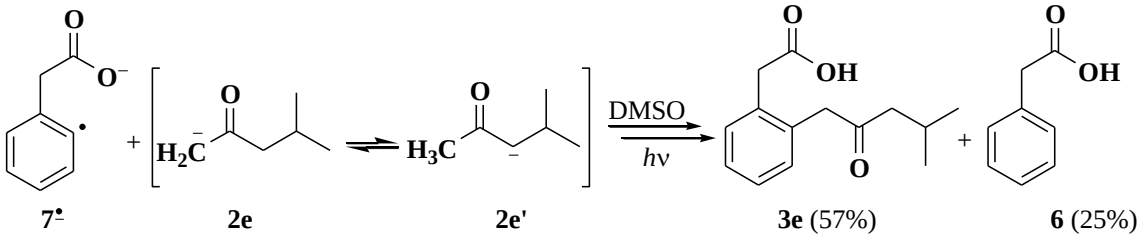


Scheme 1. Mechanism proposed for $S_{RN}1$ reaction of $\mathbf{5}^{\cdot-}$ with alkyl ketone enolate ions.



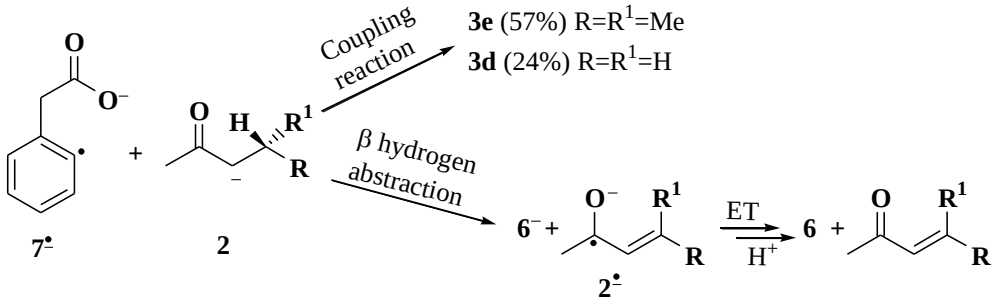
Scheme 2. Reaction of $\mathbf{7}^{\cdot-}$ with **2d** anion.

The same substitution regiospecificity was found in the reaction of $\mathbf{7}^{\cdot-}$ 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 $\mathbf{7}^{\cdot-}$ exhibits a high degree of selectivity in its coupling reaction with enolate ions.



Scheme 3. Reaction of $\mathbf{7}^{\cdot-}$ 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**$^{\bullet-}$ 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**$^{\bullet-}$ 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.



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

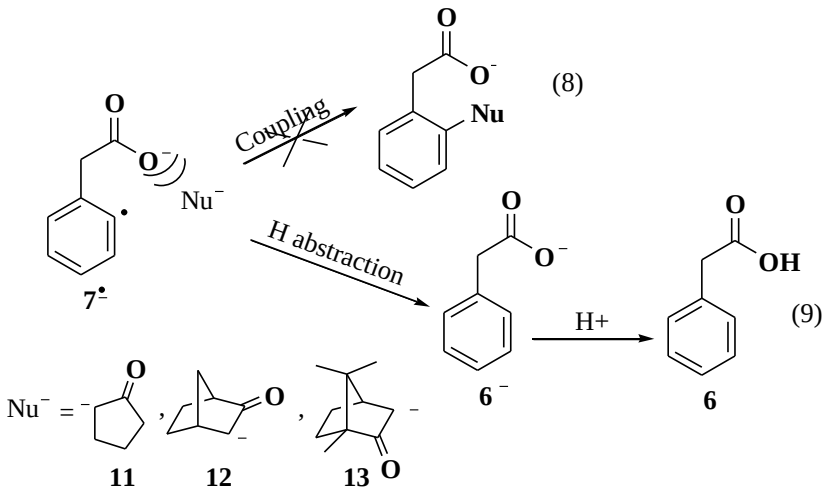
In order to determine the reactivity of **7**$^{\bullet-}$ toward secondary enolate ions, the reaction of **5**$^{-}$ with the cyclohexanone anion **2f** was studied in DMSO. This anion could not form isomeric primary enolate. In this reaction the desired ε-oxo acid **3f** was formed in 22% yield (Table 1, entry 10). When the reaction was performed in $NH_{3(l)}$ 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**$^{\bullet-}$ 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%) and **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**$^{\bullet-}$ 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).

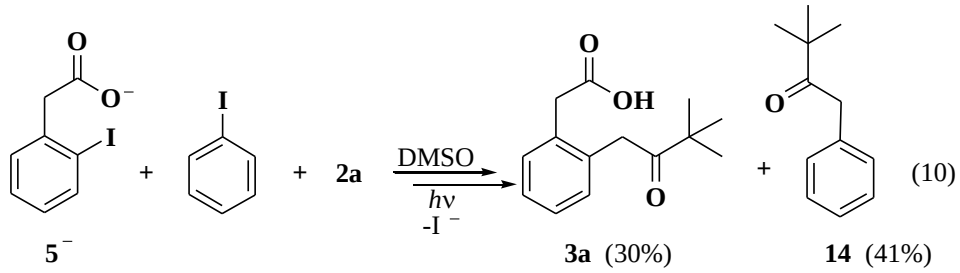
This idea is based on the fact that the analog substrate 2-iodobenzoate anion, which lacks the methylene group, reacts with cyclic enolate ions in very good yields.[24]

In order to determine the relative $S_{RN}1$ 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 $S_{RN}1$ reaction with **2a.**



Scheme 5. Competitive reactions of **7**$^{\bullet -}$. Coupling vs hydrogen abstraction for secondary enolate ions.

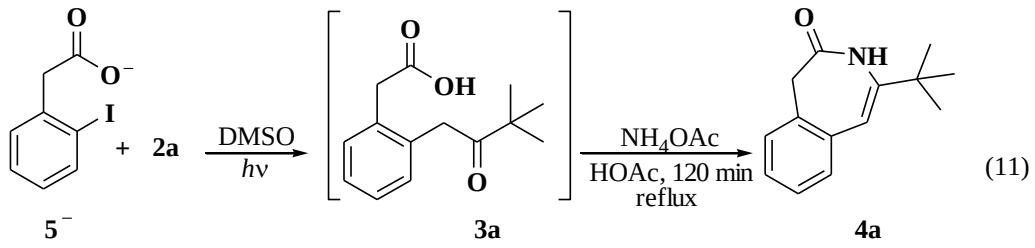


Previously, it has been determined that the relative reactivity of carbanions of aliphatic ketones toward the Ph· radical in DMSO follows the order of: cyclohexanone (0.51), pinacolone (1.00) and acetone (1.09).[25] Bearing in mind that the reactivity of acetonate ion is similar to that of pinacolone 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**$^{\bullet -}$ 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 $S_{RN}1$

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-2*H*-3-benzazepin-2-one **4a** was obtained in 69% (by ^{1}H NMR) and isolated in 59% yield respectively (equation 11; Table 2, entry 1).



(11)

Following the procedure previously described, the consecutive $S_{RN}1$-condensation reactions of **5**$^-$ 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 ^{1}H 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-1*H*-dibenzo[*b*,*d*]azepin-6(2*H*)-one **4f** was formed in 18% global yield (Table 2, entry 6).

Table 2. Synthesis of 3-benzazepin-2-ones **4a-f** by $S_{RN}1$-condensation consecutive sequence reactions through a *one-pot* procedure[a]

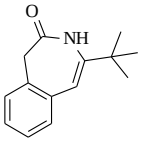
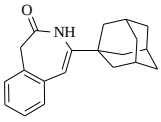
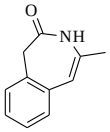
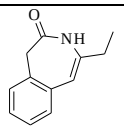
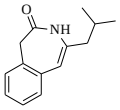
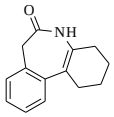
Entry	Product	ProductYield (%)[b]
1	 **4a**	**4a** (69%) [c]
2	 **4b**	**4b** (22%)
3	 **4c**	**4c** (66%)

Table 2. (continued)

Entry	Product	ProductYield (%)[b]
4	 **4d**	**4d** (18%)
5	 **4e**	**4e** (49%)
6	 **4f**	**4f** (18%)

[a]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. [b]Global yields were determined by ^{1}H NMR (internal standard method). [c]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 $S_{RN}1$ substitution reaction of $\mathbf{5}^-$ with different ketone enolate ions, followed by a condensation reaction. The use of DMSO as solvent, instead of $NH_{3(l)}$, makes this approach more versatile, practical and simple.

The $S_{RN}1$ 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 $\mathbf{7}^{\bullet-}$ exhibits a high degree of selectivity toward primary enolate ions. For this reason the enolates ions from 2-butanone and isobutyl methyl ketone exclusively afford **3d** and **3e** ε-oxo acids. Moreover, secondary enolates coupled with $\mathbf{7}^{\bullet-}$ 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_3CD 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_3CD 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_4OAc and NH_4NO_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 (λ_{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 × 50 mL). Afterwards, the last organic extract was dried over anhydrous Na_2SO_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 Na_2SO_4, filtered, and concentrated under reduced pressure. The analysis by ^{1}H 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. $NH_{3(l)}$ (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 *t*-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 $NH_{3(l)}$ and the solution was irradiatedfor 60 min The reaction was quenched with an excess of ammonium nitrate and the $NH_{3(l)}$ 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 HNO_3 and extracted with ethyl acetate (3 × 50 mL). The last organic extract was dried over anhydrous Na_2SO_4 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 ^{1}H 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.^{1}H NMR (Cl_3CD) δ1.24 (9H, s), 3.55 (2H, s), 3.94 (2H, s),7.05 (1H, m), 7.27 (3H, m). ^{13}C NMR (Cl_3CD) 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.^{1}H-^{1}H COSY NMR (Cl_3CD) δ_H/δ_H7.05/7.27.^{1}H-^{13}C HSQC NMR (Cl_3CD) δ_H/δ_C1.24/26.5, 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 $C_{14}H_{19}O_3^+$ (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. ^{1}H NMR (Cl_3CD) δ1.75 (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).^{13}C NMR (Cl_3CD) δ27.9, 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.^{1}H-^{1}H COSY NMR (Cl_3CD) δ_H/δ_H1.74/2.08, 1.91/2.08, 7.04/7.25.^{1}H-^{13}C HSQC NMR (Cl_3CD) δ_H/δ_C1.75/36.5, 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. ^{1}H-^{13}C HMBC NMR (Cl_3CD) 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 (3c).[27] Slightly yellow liquid purified by radial thin layer chromatography using petroleum ether/diethyl ether mixture (70:30→50:50) as solvent. ^{1}H NMR (Cl_3CD) 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). ^{13}C NMR (Cl_3CD) δ29.4, 38.7, 48.6, 127.7, 128.0, 131.0, 131.1, 132.6, 133.4, 176.8, 206.5. ^{1}H-^{1}H COSY NMR (Cl_3CD) δ_H/δ_H 2.16/3.79, 7.16/7.25. ^{1}H-^{13}C HSQC NMR (Cl_3CD) 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. ^{1}H-^{13}C HMBC NMR (Cl_3CD) 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, 3.79/131.1, 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).[26] Slightly yellow liquid purified by radial thin layer chromatography using petroleum ether/ethyl acetate mixture (80:20→50:50) as solvent. ^{1}H NMR (Cl_3CD) 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). ^{13}C NMR (Cl_3CD) 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. ^{1}H-^{13}C HSQC NMR (Cl_3CD) δ_H/δ_C1.02/7.7, 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. ^{1}H-^{13}C HMBC NMR (Cl_3CD) δ_H/δ_C1.02/35.4, 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. ^{1}H NMR (Cl_3CD) 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). ^{13}C NMR (Cl_3CD) 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. ^{1}H-^{1}H COSY NMR (Cl_3CD) δ_H/δ_H 0.89/2.14, 2.14/2.36, 7.15/7.26. ^{1}H-^{13}C HSQC NMR (Cl_3CD) 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. ^{1}H-^{13}C HMBC NMR (Cl_3CD) 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 $C_{14}H_{19}O_3^+$ (M+ H^+) 235.1329, found 235.1321.

[2-(2-Oxocyclohexyl)phenyl]acetic acid (3f). The crude $S_{RN}1$ reaction was used without further purification (difficult at the stage) for the synthesis of 3-benzoazepinone **4f**.

Representative procedure for one-pot synthesis of benzodiazepinones

The crude $S_{RN}1$ product mixture of acids **3** and **6** was used without purification. In a round-bottomed flask, the crude product of the $S_{RN}1$ reaction (0.150 g) was added 2 g of NH_4OAc and 4 mL of glacial acetic acid. The crude was refluxed during 120 min. After cooling and adding K_2CO_3, the crude of the reaction was extracted with ethyl acetate (3 × 50 mL). The organic

extract was dried over anhydrous Na_2SO_4 then filtered, and the solvent was removed to leave the crude products.

4-*tert*-Butyl-1,3-dihydro-2*H*-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. ^{1}H NMR (Cl_3CD) δ1.28 (9H, s), 3.45 (2H, s), 6.42 (1H, s), 6.98 (1H, s), 7.27 (4H, m).^{13}C NMR (Cl_3CD) δ29.0, 36.1, 42.7, 111.6, 127.0, 127.7, 128.2, 128.5, 131.3, 134.4, 144.9, 170.3. ^{1}H-^{13}C HSQC NMR (Cl_3CD) δ_H/δ_C 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.^{1}H-^{13}C HMBC NMR (Cl_3CD) δ_H/δ_C 1.28/29.0, 1.28/36.1, 1.28/144.9, 3.45/128.5, 3.45/131.3, 3.45/134.4, 3.45/170.3, 6.45/36.1, 6.45/127.7, 6.45/131.3, 6.45/144.9, 7.27/42.7, 7.27/111.6, 7.27/127.0, 7.27/127.7, 7.27/128.2, 7.27/128.5, 7.27/131.3, 7.27/134.4. GC-MS (*m/z*) 216 (15), **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 $C_{14}H_{18}NO^+$ (M+ H^+) 216.1383, found 216.1373.

4-(1-Adamantyl)-1,3-dihydro-2*H*-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.^{1}H NMR (CD_3COCD_3) δ1.79 (6H, t), 1.97 (6H, d), 2.09 (3H, s), 3.35 (2H, s), 6.39 (1H, s), 7.28 (4H, m), 7.83 (1H, s br).^{13}C NMR (CD_3COCD_3) δ 29.6, 37.3, 38.7, 41.4, 43.7, 111.5, 127.6, 128.5, 128.7, 129.0, 133.0, 136.1, 147.8, 170.5. ^{1}H-^{13}C HSQC NMR (CD_3COCD_3) δ_H/δ_C 1.79/37.3, 1.97/41.4, 2.09/29.6, 3.35/43.7, 6.39/111.5, 7.28/127.6, 7.28/128.5, 7.28/128.7, 7.28/129.0.^{1}H-^{13}C HMBC NMR (Cl_3CD) δ_H/δ_C 1.79/29.6, 1.79/37.3, 1.79/38.7, 1.79/41.4, 1.97/29.6, 1.97/37.3, 1.97/38.7, 1.97/41.4, 1.97/147.8, 3.35/129.0, 3.35/133.0, 3.35/136.1, 3.35/170.5, 6.39/38.7, 6.39/128.5, 6.39/128.7, 6.39/147.8, 7.28/111.5, 7.28/127.6, 7.28/128.7, 7.28/133.0, 7.27/136.1. GC-MS (*m/z*) 294 (22), **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 $C_{20}H_{24}NO^+$ (M+ H^+) 294.1852, found 294.1875.

4-Methyl-1,3-dihydro-2*H*-3-benzazepin-2-one (4c).The benzazepinone **4c** was purified by recrystallization from diethyl ether as white crystals, m.p.: 181-182 °C.^{1}H NMR (CD_3COCD_3) δ2.14 (3H, s), 3.43 (2H, s), 6.27 (1H, s), 7.24 (4H, m), 8.44 (1H, s br).^{13}C NMR (CD_3COCD_3) δ22.9, 44.1, 113.3, 127.7, 127.9, 128.4, 129.3, 131.9, 135.8, 136.2, 169.5. ^{1}H-^{13}C HSQC NMR (CD_3COCD_3) δ_H/δ_C 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.^{1}H-^{13}C HMBC NMR (Cl_3CD) δ_H/δ_C 2.14/113.3, 2.14/135.8, 3.43/129.3, 3.43/131.9, 3.43/136.2, 3.43/169.5, 6.27/22.9, 6.27/127.9, 6.27/131.9, 6.27/136.2, 7.24/127.7, 7.24/128.4, 7.24/129.3, 7.24/131.9, 7.24/136.2. GC-MS (*m/z*) 174 (12), **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 $C_{11}H_{12}NO^+$ (M+ H^+) 174.0913, found 174.0939.

4-Ethyl-1,3-dihydro-2*H*-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.^{1}H NMR (Cl_3CD) 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).^{13}C NMR (Cl_3CD) 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.^{1}H-^{13}C HSQC NMR (Cl_3CD) δ_H/δ_C1.22/12.8, 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.^{1}H-^{13}C HMBC NMR (Cl_3CD) δ_H/δ_C 1.22/29.8, 1.22/130.6, 2.35/12.8, 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). ESI-HRMS Anal. Calcd for $C_{12}H_{13}NONa^+$ (M+ Na^+) 210.0889, found 210.0906.

4-Isopropyl-1,3-dihydro-2*H*-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. ^{1}H NMR (Cl_3CD) 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).^{13}C NMR (Cl_3CD) 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. ^{1}H-^{1}H COSY NMR (Cl_3CD) δ_H/δ_H 0.96/1.87, 1.87/2.18, 7.18/7.26. ^{1}H-^{13}C HSQC NMR (Cl_3CD) δ_H/δ_C 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. ^{1}H-^{13}C HMBC NMR (Cl_3CD) δ_H/δ_C 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 $C_{14}H_{17}NONa^+$ (M+ Na^+) 238.1202, found 238.1226.

1,2,3,4,5,7-Hexahydro-6*H*-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 ºC. ^{1}H NMR (Cl_3CD) 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).^{13}C NMR (Cl_3CD) 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. ^{1}H-^{13}C HSQC NMR (Cl_3CD) δ_H/δ_C 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 $C_{14}H_{16}NO^+$ (M+ H^+) 214.1226, found 214.1237.

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

