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# Ring Splitting of Azetidin-2-ones *via* Radical Anions

**Raúl Pérez-Ruiz,[a] Jose A. Sáez,[a] Luis R. Domingo,[b] M. Consuelo Jiménez*[a] and Miguel A. Miranda*[a]**

The radical anions of azetidin-2-ones, generated by UV-irradiation in the presence of triethylamine, undergo ring-splitting via N-C4 or C3-C4 bond breaking, leading to open-chain amides. This reactivity diverges form that found for the neutral excited states, which is characterised by *α*-cleavage. The preference for *β*-cleavage is supported by DFT theoretical calculations on the energy barriers associated with the involved transition states. Thus, injection on one electron into the azetidin-2-one moiety constitutes a complementary activation strategy which may be exploited to produce new chemistry.

## Introduction

The chemistry of azetidin-2-ones has attracted considerable interest over the last decades,[1] mainly due to the important biological activity of this family of compounds (β-lactams), noteworthy their widespread clinical application as antibacterial agents.[2]

Azetidin-2-ones can be used as building blocks in organic synthesis by exploiting the possibilities of cleavage at any of the single bonds of the four-membered ring. In this context, reductive cleavage has been achieved by palladium-catalysed hydrogenolysis[3] or treatment with hydrides, whereas oxidative ring opening has been performed by treatment with ozone.[4] By contrast, the photoreactivity of azetidin-2-ones has received much less attention,[5] and in fact these compounds are generally considered nearly photostable.

Interestingly, the behaviour of radical anions of azetidin-2-ones remains unexplored, in spite of their potential to exhibit new chemistry; in fact, injection of one electron to the ring system constitutes a different (and complementary) activation strategy. Thus, photoredox catalysis via radical anions has shown potential for the development of synthetic methodologies.[6a] In addition, ring splitting of four-membered ring radical anions has been explored, both experimentally and theoretically, in connection with the repair of pyrimidine dimers in DNA by photolyases.[6b-g] With this background, the aim of the present work is to use triethylamine as donor for the generation of the radical anions of azetidin-2-ones *t*- or *c*-**1a-c** upon UV-excitation. Phenyl substitution at N, C3 and/or C4 has been chosen for convenience, in order to introduce light absorbing chromophore(s) and to contribute to the stabilisation of the radical and anionic centres developed during a possible ring splitting process.

It will be shown that the most general result is actually *β*-cleavage, leading to open-chain amides. This reactivity diverges from that found for the neutral excited states, which is characterised by *α*-cleavage. The experimental results are supported by DFT calculations on the course of the reaction at the UB3LYP/6-31+G(d) level of theory.

## Results and Discussion

In order to check the feasibility of electron transfer from $Et_3N$ to the singlet excited state of **1a-c** ($^1$**1a-c***), the fluorescence spectra of the latter were recorded in acetonitrile in the presence and in the absence of the amine. Figure 1 shows the results obtained with *c*-**1a**, as a representative example. A very week emission band was observed with maximum at ca. 340 nm, which was quenched by $Et_3N$.

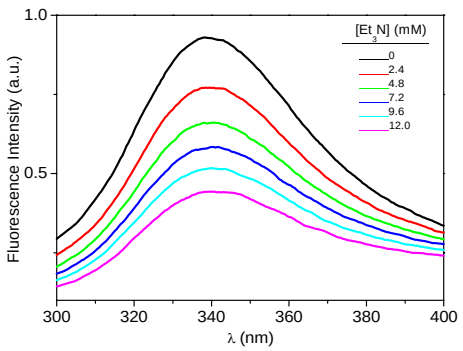
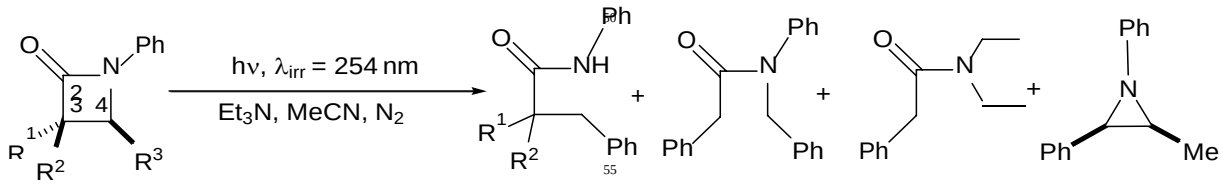



**Fig. 1** Fluorescence spectra of *c*-**1a** at 3.3 $10^{-5}$ M concentration ($\lambda_{exc}$ = 254 nm, MeCN, air) in the presence of increasing amounts of $Et_3N$, from 0 to 12 mM.

From the intersection between the normalised emission and excitation bands, a singlet energy of 95 kcal $mol^{-1}$ was determined. Furthermore, the reduction potential was measured by means of cyclic voltammetry[7] and found to be -2.6 V vs SCE, in acetonitrile. With these data, application of the Rehm-Weller




*t*-**1a**: $R^1$ = Ph; $R^2$ = H; $R^3$ = Ph
*c*-**1a**: $R^1$ = H; $R^2$ = Ph; $R^3$ = Ph
*t*-**1b**: $R^1$ = cyclopropyl; $R^2$ = H; $R^3$ = Ph
*c*-**1b**: $R^1$ = H; $R^2$ = cyclopropyl; $R^3$ = Ph
*t*-**1c**: $R^1$ = Ph; $R^2$ = H; $R^3$ = Me
*c*-**1c**: $R^1$ = H; $R^2$ = Ph; $R^3$ = Me

**Scheme 1**

equation[8] confirmed that electron transfer from $Et_3N$ to $^1$**1a-c*** is indeed exergonic ($\Delta G$ = -15 kcal $mol^{-1}$). For product studies, acetonitrile solutions of *t*-**1a-c** or *c*-**1a-c** containing a 50-fold excess of triethylamine were deaerated with nitrogen and irradiated through quartz for 2 hours, with low pressure mercury lamps ($\lambda_{irr}$ = 254 nm). The reaction mixtures were analysed by GC-MS, using biphenyl as internal standard; the results are shown in Scheme 1 and Table 1. In general, mass balances were expectedly poor for high conversions, due to the extensive production of radicals and polymers derived therefrom. In the case of *t*-**1a** or *c*-**1a**,[9] with three vicinal phenyl groups at N, C3 and C4, only the open chain amides **2a**[10] and **3a**[11] were obtained as products. Their chemical structures were confirmed by comparison with authentic samples.

**Table 1** Photolysis of **1a-c** in the presence of triethylamine[a]

| Compound | Conv[b] (%) | MB[c] (%) | Product Distribution[d] (%) | | | |
|---|---|---|---|---|---|---|
| | | | **2** | **3** | **4** | **5** |
| *t*-**1a** | 91 | 30 | 73 | 27 | - | - |
| *c*-**1a**[e] | 84 | 27 | 52 | 48 | - | - |
| *t*-**1b** | 80 | 30 | 100 | - | - | - |
| *c*-**1b** | 68 | 48 | 100 | - | - | - |
| *t*-**1c** | 47 | 87 | - | - | 100 | - |
| *c*-**1c** | 36 | 95 | - | - | 54 | 46 |

[a] **1a-c** = 0.05 mmol, $Et_3N$ = 2.5 mmol, MeCN = 5 mL, $N_2$, $\lambda_{irr}$ = 254 nm; [b] Calculated from recovered **1a-c**; [c] Mass balance; [d] Determined by GC MS using biphenyl as internal standard; errors were lower than 5% of the stated values; [e] This reaction was also carried out with *N,N*-dimethylcyclohexylamine as electron donor with similar results.

When azetidin-2-ones *t*-**1b** and *c*-**1b** were photolysed in the presence of triethylamine only **2b**, with the unaltered cyclopropyl ring, was detected as a result of N-C4 bond cleavage. The product was isolated by HPLC and fully characterised by $^1$H-NMR, $^{13}$C-NMR and MS, as well as by X-Ray diffraction analysis (see Figure 2).

To check whether the absence of phenyl groups in vicinal positions of the ring has any influence on the reactivity of the radical anions, azetidin-2-ones *t*-**1c** and *c*-**1c** were selected. Interestingly, their photolysis in the presence of triethylamine did not afford the expected open chain amides; instead, *t*-**1c** and *c*-**1c** reacted sluggishly, to give only products arising from fragmentation (**4c**)[12] and decarbonylation (**5c**).[13]

In the absence of triethylamine, under otherwise identical experimental conditions, the photoreactions of *t*-**1a,b** and *c*-**1a,b** were markedly slower and gave N-benzylideneaniline as the only detectable product. This is obviously the result of N-C2 plus C3-C4 bond cleavage. As regards *t*-**1c** and *c*-**1c**, the absence of triethylamine did not result in significant changes, except for the lack of **4c**, whose formation can be attributed to nucleophilic trapping of phenylketene by the tertiary amine with concomitant loss of ethylene.[14] Again, the decarbonylation product was only observed in the case of the *cis* isomer, probably because the steric strain introduced by the substituents at C3 and C4 results in a slight disruption of the planar geometry of the precursor biradical generated by cleavage of the N-C2 bond, difficulting formation of the ketene-imine pair. Thus, it seems that, even in the presence of triethylamine, the reactions of *t*-**1c** and *c*-**1c** proceed directly from the neutral excited state, rather than from the radical anion. This was confirmed by photolysis of *t*-**1c** in methanol, which led to formation of methyl phenylacetate, the trapping product of phenylketene. In agreement with expectations, in the case of *c*-**1c** aziridine **5c** was also obtained.

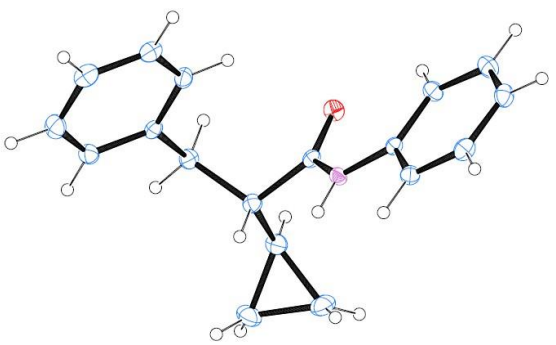
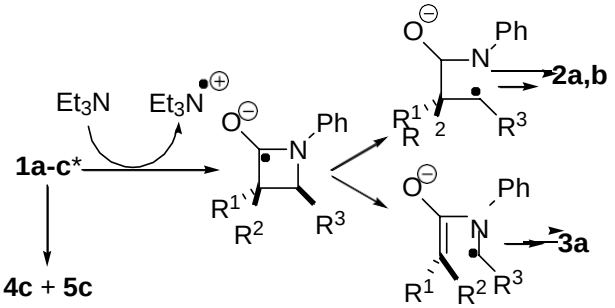


**Fig. 2** X-Ray structure of the amide-like compound **2b**

A mechanistic rationalization of the obtained results is summarized in Scheme 2. After excitation of azetidin-2-ones to the singlet excited states, $^1$**1a-c*** would accept one electron from $Et_3N$, to afford the corresponding radical anions **1a-c**$^{\bullet-}$. Subsequent $\beta$-cleavage of the N-C4 or the C3-C4 bonds would lead to the distonic radical anionic intermediates and ultimately to

the open-chain amides **2a,b** or **3a**. In the case of **1c**, direct photolysis would ensue with *α*-cleavage, affording **4c** and **5c**.




**Scheme 2.** Mechanistic pathways for ring splitting of the radical anions generated by photolysis of azetidin-2-ones in the presence of triethylamine

To understand the reactivity of radical anions *t*-**1a-c**$^{\bullet -}$ and *c*-**1a-c**$^{\bullet -}$, theoretical calculations based on DFT methods at the UB3LYP/6-31+G(d)[15] level of theory were performed. Solvent effects were considered through single-point calculations at gas-phase stationary geometries, using the self-consistent reaction field (SCRF) method based on the polarizable continuum model (PCM) of Tomasi's group.[16]

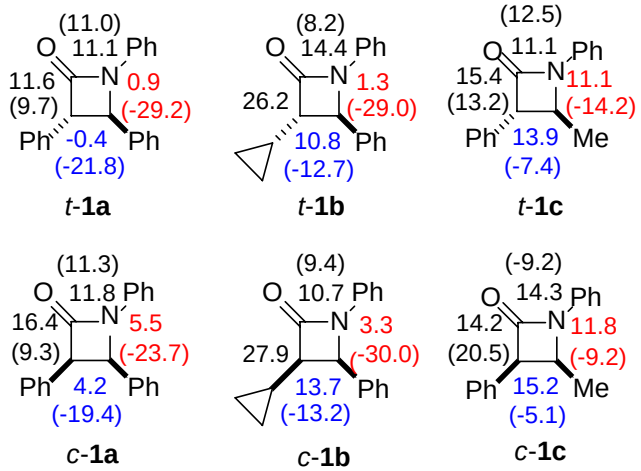
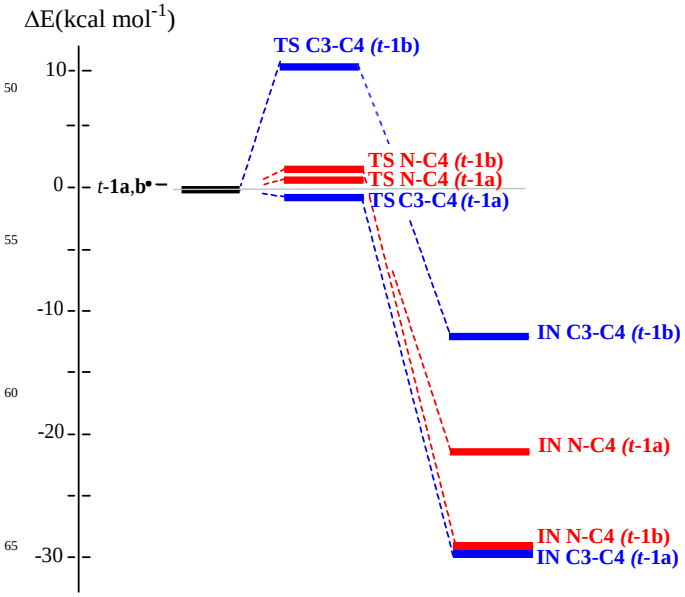



**Fig. 3.** UB3LYP/6-31+G(d) relative energies (kcal mol$^{-1}$), in acetonitrile, associated with the transition states (and, in parentheses, the intermediates) for all the bond-breaking processes at the radical anions *t*- and *c*-**1a-c**$^{\bullet -}$

Four possible ring splitting pathways can be envisaged, namely N-C2, C2-C3, C3-C4 and N-C4 (see Figure 3). In *c*- and *t*-**1a**$^{\bullet -}$, with three vicinal phenyl groups, the most favourable cleavages are those associated with the N-C4 and C3-C4 bonds. Accordingly, a mixture of the corresponding open chain products (**2a** and **3a**) was indeed obtained. At the radical anions *c*- and *t*-**1b**$^{\bullet -}$, with two adjacent phenyl groups, cleavage of the N-C4 bond is clearly favoured. This is in agreement with the fact that only one open chain product (**2b**) was experimentally obtained. Finally, the barriers associated with the four bond-breaking processes at *c*- and *t*-**1c**$^{\bullet -}$ are considerably higher, so no product was detected arising from the radical anion. In general, formation of intermediates via N-C4 or C3-C4 bond-breaking is exothermic (-13 to -22 kcal mol$^{-1}$). A summarised energy diagram containing the data calculated for the most favourable reaction pathways of *t*-**1a,b**$^{\bullet -}$ is shown in Scheme 3. A very similar trend is exhibited by the corresponding *cis* isomers.




**Scheme 3.** Relative energies of the transition states and intermediates involved in ring splitting of *t*-**1a,b**$^{\bullet -}$

The geometries of the intermediates involved in the ring splitting of **1a,b**$^{\bullet -}$ are shown in Figure 4. In all cases, the breaking bond is markedly elongated at this stage and, accordingly, the bond order is nearly zero. As regards location of charge and spin, the highest accumulation of negative charge is found in the carbonyl-containing substructure (N-C2=O or C3-C2=O, depending on whether ring splitting occurs at the C3-C4 or N-C4 bonds, respectively). Finally, the maximum value of spin density is always found at C4. The rest of charge and spin is spread all over the structure, mainly due to delocalisation through the phenyl rings.

## Conclusions

In summary, ring splitting of azetidin-2-ones via their radical anions proceeds with *β*-cleavage of the N-C4 and/or the C3-C4 bonds, leading to open chain amides. Theoretical DFT calculations have allowed us to characterise the involved transition states and intermediates, which support the experimentally observed reactivity. It has been shown that injection of one electron into the azetidin-2-one moiety constitutes a complementary activation strategy, which may be exploited to produce new chemistry.

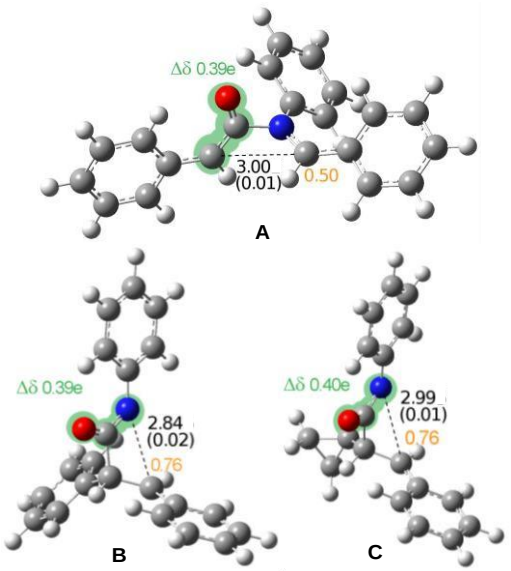



**Fig. 4.** Calculated geometries for the intermediates involved in the ring splitting processes of **1a,b**$^{\bullet -}$. Key bond distances (in Angstroms) and bond order values (in parenthesis) are indicated in black. **A**: IN C3-C4 (*t*-**1a**), **B**: IN N-C4 (*t*-**1a**); **C**: IN N-C4 (*t*-**1b**). Natural charge accumulated at N-C2=O or C3-C2=O moiety with respect to the corresponding neutral azetidin-2-one, is indicated in green. The Mulliken spin density at C4 is given in orange.

## Materials and Methods

### Synthesis of the new compounds

Azetidin-2-ones *t*-**1a** and *c*-**1a**, have been previously described and characterised.[9] Compounds *t*-**1b**, *c*-**1b**, *t*-**1c** and *c*-**1c** were synthesised according to a procedure previously published for related compounds.[17] Briefly, in the case of *t*-**1b** and *c*-**1b**, a solution of cyclopropylacetylene (2.0 mmol, 132 mg) in DMF/pyridine (8 mL/2mL) was added to a mixture of *N*-*α*-diphenylnitrone (2.0 mmol, 400 mg), CuI (0.2 mmol, 95 mg) and $K_2CO_3$ (2.2 mmol, 300 mg). The resulting mixture was stirred overnight at room temperature under $N_2$ atmosphere, poured into water and extracted with diethyl ether. The organic phase was dried over $Na_2SO_4$ and the solvent evaporated under vacuum. The residue was submitted to column chomatography on silica gel, using hexane/ethyl acetate as eluent (99:1 to 90:10), to afford *t*-**1b** and *c*-**1b**.

A similar procedure was followed for the synthesis of *t*-**1c** and *c*-**1c**, using phenylacetylene (2.0 mmol, 204 mg) and *N*-phenyl-*α*-(methyl)nitrone as reactants. The latter was generated *in situ* by addition of acetaldehyde (2.4 mmol, 105 mg) in 3 mL of $Et_2O$ to a mixture of *N*-phenylhydroxylamine (2.4 mmol, 262 mg) and $K_2CO_3$ (5 mmol, 690 mg) in 3 mL of $Et_2O$ at 0 ºC, during 1 h.

Photoproduct **2b** was obtained as follows: *t*-**1b** (0.05 mmol, 13.2 mg) was irradiated in the presence of $Et_3N$ (2.5 mmol, 252 mg) for 2 h, using MeCN (5 mL) as solvent. After evaporation of the solvent, final purification was done by HPLC (acetonitrile:water 80:20 v/v) and recrystallization in hexane.

### Characterisation of the new compounds

All new compounds were characterised by $^1$H and $^{13}$C NMR spectroscopy, as well as by high resolution mass spectrometry (HRMS). Their purity was confirmed by gas chromatography (GC) and high performance liquid chromatograpy (HPLC). A summary of the most relevant data follows.

***trans*-3-Cyclopropyl-1,4-diphenylazetidin-2-one (*t*-1b)**

$^1$H-NMR (300 MHz, $CDCl_3$) (δ, ppm): 0.05 (m, 2H), 0.39 (m, 3H), 3.08 (m, 1H), 5.12 (d, 1H, *J* = 5.9 Hz), 6.98 (m, 1H), 7.25 (m, 9H); $^{13}$C-NMR (75 MHz, $CDCl_3$) (δ, ppm): 2.5, 3.8, 6.7, 58.8, 59.5, 117.1, 123.7, 126.9, 127.8, 128.4, 128.9, 135.6, 137.7, 166.7; Exact Mass (HRMS): required for $C_{18}H_{17}NO$: 264.1388 ($MH^+$); found 264.1384.

***cis*-3-Cyclopropyl-1,4-diphenylazetidin-2-one (*c*-1b)**

$^1$H-NMR (300 MHz, $CDCl_3$) (δ, ppm): 0.38 (m, 2H), 0.58 (m, 2H), 1.13 (m, 1H), 2.77 (dd, 1H, *J* = 2.5 Hz, *J* = 7.9 Hz), 4.69 (d, 1H, *J* = 2.5 Hz), 6.96 (m, 1H), 7.24 (m, 9H); $^{13}$C-NMR (75 MHz, $CDCl_3$) (δ, ppm): 2.2, 3.2, 9.4, 61.0, 63.9, 117.0, 123.7, 125.6, 128.3, 129.0, 129.1, 137.7, 138.0, 166.5; Exact Mass (HRMS): required for $C_{18}H_{17}NO$: 264.1388 ($MH^+$); found 264.1393.

***trans*-1,3-Diphenyl-4-methylazetidin-2-one (*t*-1c)**

$^1$H-NMR (400 MHz, $CDCl_3$) (δ, ppm): 1.12 (d, J = 6.3 Hz, 3H), 4.51 (p, *J* = 6.3 Hz, 1H), 4.71, (d, *J* = 6.0 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.29-7.50 (m, 9H); $^{13}$C-NMR (100 MHz, $CDCl_3$) (δ, ppm): 15.2, 52.4, 57.9, 117.2, 124.1, 127.8, 128.8, 129.3, 129.4, 132.9, 137.7, 165.6; Exact Mass (HRMS): required for $C_{16}H_{15}NO$: 238.1232 ($MH^+$); found 238.1233.

***cis*-1,3-Diphenyl-4-methylazetidin-2-one (*c*-1c)**

$^1$H-NMR (400 MHz, $CDCl_3$) (δ, ppm): 1.67 (d, *J* = 6.0 Hz, 3H), 4.04 (d, *J* = 2.3 Hz, 1H), 4.16, (dq, *J* = 6.0 Hz, *J* = 2.3 Hz, 1H), 7.13, (t, *J* = 7.3 Hz, 1H), 7.29-7.46 (m, 9H); $^{13}$C-NMR (100 MHz, $CDCl_3$) (δ, ppm): 18.4, 56.7, 62.2, 117.3, 124.1, 127.5, 127.8, 129.1, 129.4, 135.2, 137.4, 165.2; Exact Mass (HRMS): required for $C_{16}H_{15}NO$: 238.1232 ($MH^+$); found 238.1220.

**2-Cyclopropyl-N,3-diphenylpropanamide (2b)**

$^1$H-NMR (300 MHz, $CDCl_3$) (δ, ppm): 0.08 (m, 1H), 0.24 (m, 1H), 0.57 (m, 2H), 1.01 (m, 1H), 1.68 (m, 1H), 3.04 (m, 2H), 7.01 (m, 1H), 7.20 (m, 9H); $^{13}$C-NMR (75 MHz, $CDCl_3$) (δ, ppm): 4.3, 4.8, 13.4, 38.7, 55.4, 120.1, 124.2, 126.2, 128.3, 128.8, 129.1, 137.6, 139.5, 172.6; Exact Mass (HRMS): required for $C_{18}H_{19}NO$: 266.1545 ($MH^+$); found 266.1548. The X-Ray structure and data of **2b** are deposited in the Cambridge Crystallographic Data Centre (CCDC 860535 & 860536).

**Computational methods**

DFT calculations have been performed using B3LYP exchange-

correlation functional together with the standard 6-31+G(d) basis set.[15] For the studied open-shell species, the spin-unrestricted formalism (UB3LYP) was employed. The S2 expectations for the doublet states of all radical anions showed an ideal value of 0.750 after spin annihilation, so the geometries and the energetics are reliable for this study. Optimizations were carried out using the Berny analytical gradient optimization method.[18] The stationary points were characterized by frequency calculations in order to verify that the transition structures (TSs) had only one imaginary frequency. The intrinsic reaction coordinate (IRC)[19] path was traced in order to check the energy profiles connecting each TS with the two associated minima of the proposed mechanism, using the second order González-Schlegel integration method.[20] The electronic structures of stationary points were analysed by the natural bond orbital (NBO) method.[21] The solvent effects on the mechanism of the ring splitting have been considered through UB3LYP/6-31+G(d) single-point calculations at gas-phase stationary geometries using self-consistent field reaction field (SCRF)[16] method based on the polarizable continuum model (PCM) of Tomasi's group.[16] As the solvent used in the experimental work was acetonitrile, we have selected its dielectric constant ε = 36.64. Thermodynamic calculations were made with the standard statistical thermodynamics at 298.15 K and 1 atm. Harmonic vibrational frequencies were scaled by a factor of 0.96.[22] All calculations were carried out with the Gaussian09 suite of programs.[23]

## Acknowledgements

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## Notes and references

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† Electronic Supplementary Information (ESI) available: [Spectroscopic characterization, X-Ray data of **2b**, and geometries of the stationary points involved in several reactions; UB3LYP/6-31+G(d) Cartesian coordinates (78 pp.)]. See DOI: 10.1039/b000000x/

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