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Photochemistry of 3-Substituted Bicyclo[3.1.0]hex-3-en-2-ones. Regioselective Synthesis of *Ortho*-Substituted Phenols by Pauson–Khand Reaction

Iolanda Marchueta, Santiago Olivella, Lluís Solà, Albert Moyano,
Miquel A. Pericàs,*,† and Antoni Riera*

Departament de Química Orgànica, Martí i Franquès, 1-11, Barcelona E-08028, Spain

a.riera@qo.ub.es

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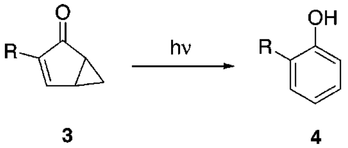
ABSTRACT



3-Substituted bicyclo[3.1.0]hex-3-en-2-ones 3, easily obtained by Pauson–Khand reaction between terminal alkynes and cyclopropene, have been quantitatively converted into *ortho*-substituted phenols 4 by irradiation with UV light (350 nm). The kinetics and mechanism of this photochemical process have been studied by means of FT-IR and semiempirical (AM1 3x3 CI) calculations.

Some terpenes bearing a bicyclo[3.1.0]hex-3-en-2-one skeleton such as umbellulone (**1**) are present in essential oils of many plants.[1] Besides these natural products, several compounds with the same bicyclic structure have been prepared,[2] most commonly by photorearrangement of cyclohexenones,[3] phenols,[4] or cyclohexadienones.[5] The latter transformation, originally found in the conversion of santonin to lumisantonin, has been the subject of extensive mechanistic studies[5,6] Much less information is known about the photochemical rearrangement of bicyclo[3.1.0]hex-3-en-2-ones into phenols, which was observed by Eastman[7] in 1959 when he reported that the irradiation of neat umbellulone (**1**) gave thymol (**2**) (Scheme 1). The difficult availability of these

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[†] E-mail: mapericas@qo.ub.es.

(1) (a) Gillam, A. E.; West, T. F. *J. Chem. Soc.* **1945**, 95−98. (b) Wheeler, J. W.; Chung, R. H. *J. Org. Chem.* **1969**, *34*, 1149−1151.

(2) (a) Parziale, P. A.; Berson, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 4595−4606. (b) Dolbier Jr., W. R.; Garza, O. T. *J. Org. Chem.* **1978**, *43*, 3848. (c) Baraldi, P. G.; Pollini, G. P.; Simoni, D.; Barco, A.; Benetti, S. *Tetrahedron* **1984**, *40*, 761−764. (d) Padwa, A.; Chiacchio, U.; Fairfax, D. J.; Kassir, J. M.; Litrico, A.; Semones, M. A.; Xu, S. L. *J. Org. Chem.* **1993**, *58*, 6429−6437. (e) Williamson, B. L.; Tykwinski, R. R.; Stang, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 93−98.

(3) (a) Zimmerman, H. E.; Zhu, Z. *J. Am. Chem. Soc.* **1995**, *117*, 5245−5262. (b) Schuster, D. I.; Brown, R. H.; Resnick, B. M. *J. Am. Chem. Soc.* **1978**, *100*, 4504−4512. (c) Dauben, W. G.; Spitzer, W. A.; Kellogg, M. S. *J. Am. Chem. Soc.* **1971**, *93*, 3674−3677.

(4) (a) Kakiuchi, K.; Ue, M.; Yamaguchi, B.; Nishimoto, A.; Tobe, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3468−3470. (b) Baeckström, P.; Jacobsson, U.; Koutek, B.; Norin, T. *J. Org. Chem.* **1985**, *50*, 3728−3732.

(5) (a) Zimmerman, H. E.; Schuster, D. I. *J. Am. Chem. Soc.* **1961**, *83*, 4486−4488. (b) Zimmerman, H. E. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 1−11. (c) Schultz, A. G.; Lavieri, F. P.; Macielag, M. *Tetrahedron Lett.* **1986**, *27*, 1481−1484. (d) Schultz, A. G. *Pure Appl. Chem.* **1988**, *60*, 981−988. (e) Zimmerman, H. E.; Lynch, D. C. *J. Am. Chem. Soc.* **1985**, *107*, 7745−7756. (f) Quinkert, G.; Kleiner, E.; Freitag, B. J.; Glenneberg, J.; Billhardt, U. M.; Cech, F.; Schmieder, K. R.; Schudok, C.; Steinmetzer, H. C.; Bats, J. W.; Zimmermann, G.; Dürner, G.; Rehm, D.; Paulus, E. F. *Helv. Chim. Acta* **1986**, *69*, 469−537.

(6) (a) Schuster, D. I. *Acc. Chem. Res.* **1978**, *11*, 65−73. (b) Quinkert, G.; Scherer, S.; Reichert, D.; Nestler, H. P.; Wennemers, H.; Ebel, A.; Urbahns, K.; Wagner, K.; Michaelis, K. P.; Wiech, G.; Prescher, G.; Bronstert, B.; Freitag, B. J.; Wicke, I.; Lisch, D.; Belik, P.; Crecelius, T.; Horstermann, D.; Zimmermann, G.; Bats, J. W.; Durner, G.; Rehm, D. *Helv. Chim. Acta* **1997**, *80*, 1683−1772. And references therein.

(7) (a) Wheeler, J. W.; Eastman, R. H. *J. Am. Chem. Soc.* **1959**, *81*, 236−237. (b) Barber, L.; Chapman, O. L.; Lassila, J. D. *J. Am. Chem. Soc.* **1968**, *90*, 5933−5934.

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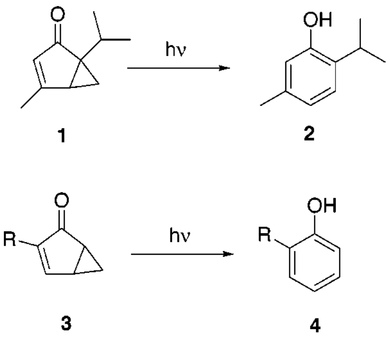
Scheme 1



bicyclic compounds has reduced the study of their photochemical behavior to few cases.[8] Nevertheless, during the preparation of the previously unknown 3-substituted-bicyclo-[3.1.0]hex-3-en-2-ones **3**[9] by Pauson−Khand cyclization,[10] we observed that enones **3** slowly isomerized on standing into the corresponding *ortho*-substituted phenols **4**. Taking into account the now easy availability of these bicyclic adducts **3**, we decided to explore the synthetic utility of this transformation and to start a mechanistic study on it. We report here our results on the isomerization of 3-substituted-bicyclo[3.1.0]hex-3-en-2-ones **3** into 2-substituted phenols **4**.

After the initial observation of the conversion of **3** into **4**, we decided to unambiguously establish the origin of the isomerization. A literature survey indicated that, besides the photochemical rearrangement, there were some reports in which a similar transformation was catalyzed by acid or base.[11] Therefore, 3-(triphenylsilyl)bicyclo[3.1.0]hex-3-en-2-one (**3d**) was selected as a representative compound and was submitted to several acidic, basic, and radical-forming conditions (CH_2Cl_2/pTsOH; MeOH/HCl; Amberlist 15, NaOH, PBO/NBS). In all cases, most of the starting material was recovered unchanged. On the other hand, the exposure of **3d** to direct sunlight (either neat or in solution) for 72 h cleanly afforded 2-(triphenylsilyl)phenol (**4d**) in quantitative yield, firmly establishing the photochemical nature of the transformation. Consequently, to perform the reaction in a reproducible manner, a series of reactions were conducted in a Rayonet reactor and monitored with an FT-IR instrument. The reactions were clean and fast, and the analysis of selected bands in the IR spectra of starting material and reaction product allowed the easy monitoring of the reaction process. As expected, irradiation of bicyclic adducts **3a**−**f** in $CHCl_3$ at 350 nm afforded *ortho*-substituted phenols **4a**−**f** in nearly quantitative yields as shown in Table 1. According to the FT-IR studies, the photorearrangement at 35 °C took place without any detectable intermediate following a first-order rate law. The rate constants could not be accurately measured because of the self-quenching produced by the high concentrations necessary for IR monitoring. Nevertheless, it could be clearly observed that the rate of isomerization of compounds **3b** and **3d** was faster than that of the other adducts (Figure 1).

Table 1. Photochemical Transformations of Bicyclo[3.1.0]hex-3-en-2-ones **3** into *Ortho*-Substituted Phenols **4**

	starting adduct, R =	**4**, % yield
3a	*tert*-butyl	98
3b	*p*-F-C_6H_4	96
3c	*n*-hexyl	99
3d	Ph_3Si	97
3e	$PhCH_3C(OH)$	96
3f	$(CH_3)_2C(OH)$	99

[a] Reaction conditions. A solution of 0.7 mmol of Pauson−Khand adducts **3** in 0.5 mL of $CHCl_3$ was irradiated in a Rayonet reactor equipped with 16 lamps of 350 nm, with the reaction monitored by FT-IR using a React IR-1000 (Applied systems). When the reaction was complete, the solution was chromatographed on SiO_2.

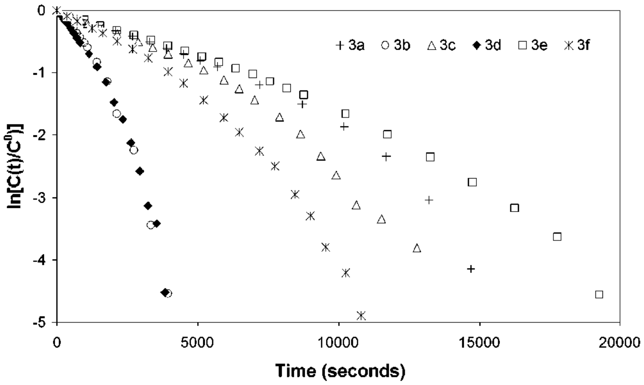


Figure 1. Kinetic plots [ln($C(t)/C_0$) against time (s)] for the rearrangement of adducts **3a**−**d** into phenols **4a**−**d.** Concentrations were taken from FT-IR data.

From a synthetic point of view, the combination of the Pauson−Khand reaction and photorearrangement constitutes a new general procedure for the completely regioselective synthesis of *ortho*-substituted phenols, starting from terminal alkynes **5** (Scheme 2).

A plausible mechanism for this transformation should involve the cleavage of the internal cyclopropane bond to afford a short-lived intermediate, followed by a proton migration to the tautomeric keto form of phenol. The nature

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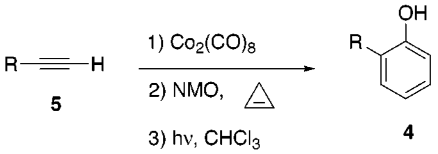
[8] (a) Dauben, W. G.; Hecht, S. *J. Org. Chem.* **1998**, *63*, 6102−6107. (b) Zimmerman, H. E.; Sebek, P.; Zhu, Z. *J. Am. Chem. Soc.* **1998**, *120*, 8549−8550. (c) Zimmerman, H. E.; Keese, R.; Nasielski, J.; Swenton, J. S. *J. Am. Chem. Soc.* **1966**, *88*, 4895−4903.

[9] Marchueta, I.; Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A. *Org. Lett.* **2001**, *3*, 3193−3196.

[10] For recent reviews, see: (a) Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, pp 1037−1064. (b) Chung, Y. K. *Coor. Chem. Rev.* **1999**, *188*, 297−341. (c) Sugihara, T.; Yamaguchi, M.; Nishizawa, M. *Rev. Heteroat. Chem.* **1999**, *21*, 179−194. (d) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263−3283.

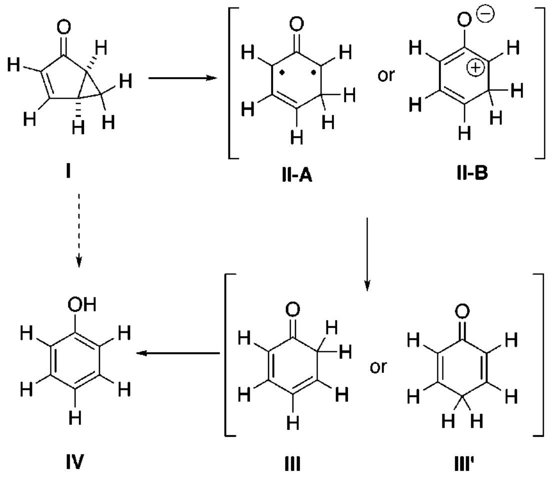
[11] (a) Childs, R. F.; George, B. E. *Can. J. Chem.* **1988**, *66*, 1350−1354. (b) Rajakumar, P.; Satheeshkumar, K. *Synth. Commun.* **1995**, *25*, 2561−2568.

Scheme 2



of this key intermediate, however, was unclear since, according to literature precedents, it could be either a zwitterionic[12] or a diradical species[6a] (Scheme 3). At this point, we decided to perform a theoretical study to get a detailed picture of this rearrangement. The photochemical transformation of bicyclo[3.1.0]hex-3-en-2-one **I** (**3**, R = H) into phenol **IV** was chosen as a model reaction. The calculations were performed using the semiempirical SCF-MO method AM1[13] as implemented in the MOPAC6 program.[14] To have an adequate description of both triplet and singlet states, the calculations were performed using the 3x3 configuration interaction (CI) on the basis of the molecular orbitals given by the "half electron method" [15] as suggested by Salem and Rowland.[16]

Scheme 3



According to well-established photochemical mechanisms, we assumed that irradiation at 350 nm would promote **I** to its singlet excited state $S_1(n-\pi^*)$ which then would lead to the $\pi-\pi^*$ triplet state through an ISC. This **I**-$T_1(\pi-\pi^*)$ intermediate was located at the AM1 3x3 CI level 50.6 kcal/mol above the ground state. Elongation of the internal cyclopropane bond in this triplet structure allowed the location and characterization of transition state TS-1 only 7.2 kcal/mol above **I**-T_1. The transition state TS-1 connected with the intermediate **II** which was optimized at the same level of theory (AM1 3x3 CI) in its singlet and triplet states. Both electronic states were found to be very close in energy, with the triplet only 1.0 kcal/mol more stable (Figure 2).

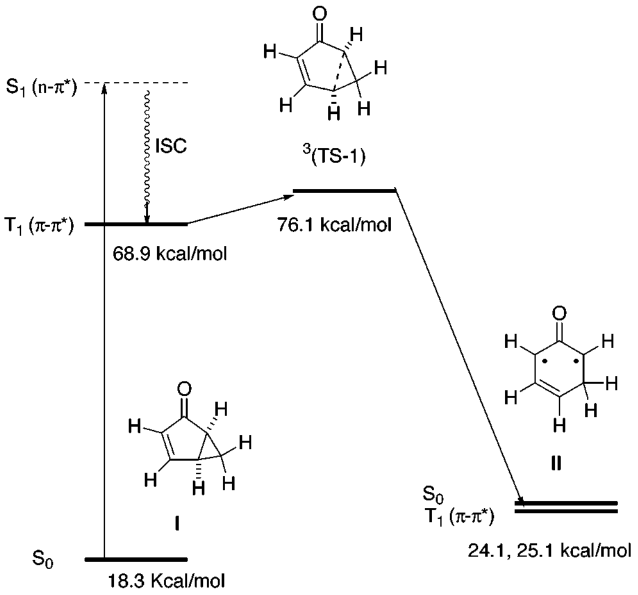


Figure 2. Schematic representation of the reaction pathway for the rearrangement of **I** into intermediate **II**, showing the enthalpy of formation (AM1 3x3 CI) of the stationary points.

The geometry and electronic structure of **II**, either in the singlet or the triplet state, indicated that it is in fact a true diradical (**II-A**) and not a zwitterionic species (**II**−**B**) (Scheme 3). The diradical nature of the singlet state of **II** as well as the nearly degenerated energy of both states of **II** confirmed the need of a configuration interaction treatment for a correct description of these structures. Moreover, the proximity of both potential hypersurfaces near this point let us to think that the second ISC should take place around the intermediate returning to the singlet state. Consequently the second part of the reaction pathway was explored in the singlet potential hypersurface.

Assuming that the second part of the reaction coordinate would take place in the singlet hypersurface, the transformation from **II**-S_0 into **IV** can occur by migration of a hydrogen atom to either vicinal carbon 2 or 4, leading to intermediates **III** or **III′**. Both transition states were located and characterized at the AM1 3x3 CI level of theory. The transition state TS-2 corresponding to the C3−C2 migration turned out to be 4.1 kcal/mol more stable than the one corresponding to the C3−C4 migration. Therefore, the minimum energy reaction path involves ketone **III** which is in fact a tautomer of phenol **IV** (Figure 3).

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[12] The classic mechanism postulated by Zimmerman of the photolysis of 6,6-diphenylbicyclo[3.1.0]hexen-2-one involves a ground-state zwitterionic intermediate. See: (a) Zimmerman, H. E.; Epling, G. A. *J. Am. Chem. Soc.* **1972**, *94*, 7806−7811 and refs 5 and 6.

[13] Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902−3909

[14] As implemented in Cerius2, version 3.8. Molecular simulations, San Diego, 1998.

[15] Dewar, M. J. S.; Hashmall, J. A.; Vernier, C. G. *J. Am. Chem. Soc.* **1968**, *90*, 1953−1957.

[16] Salem, L.; Rowland, C. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 92−111.

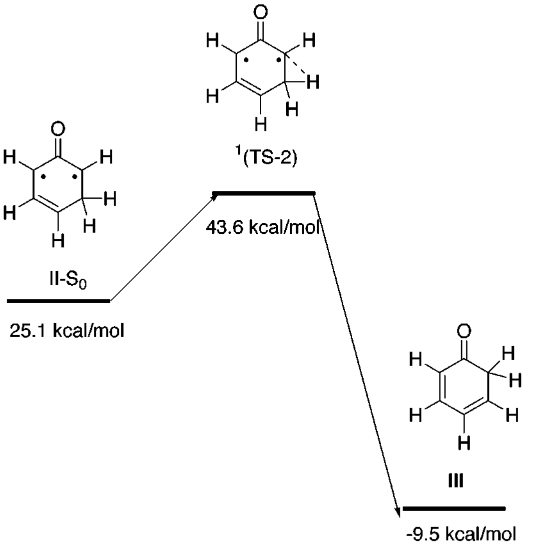

Figure 3. Reaction coordinate for the conversion of **II** into **III**, showing the enthalpy of formation (AM1 3x3 CI) of the stationary points.

In summary, the photochemical rearrangement of 3-substituted bicyclo[3.1.0]hex-3-en-2-ones to *ortho*-substituted phenols has been studied both from the experimental and theoretical points of view. The mechanism of the rearrangement has been studied in detail at the semiempirical 3x3 CI AM1 level. According to these calculations, the fission of the internal σ bond in the bicyclic adduct would take place easily in the triplet state, leading to a diradical intermediate. After an ISC from the triplet to singlet hypersurface, a hydrogen migration from C3 to C2 would lead to the ketonic tautomer of the corresponding phenol. A complete ab initio study of this reaction coordinate will be published elsewhere.

From an experimental point of view, a new procedure for the regioselective synthesis of *ortho*-substituted phenols has been developed. The sequence consists of a Pauson−Khand reaction of terminal alkynes and cyclopropene followed by photochemical isomerization of the corresponding adducts. The photochemical process can take place under sunlight exposition or by irradiation at 350 nm, and the yields are quantitative in both cases. A schematic representation of the origin of the phenol fragments is shown in Figure 4.

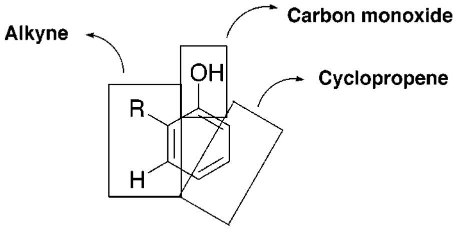

Figure 4.

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