JOC*Note*

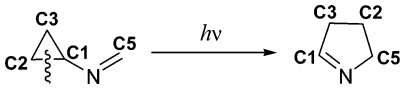
The *N*-Cyclopropylimine-1-pyrroline Photorearrangement as a Synthetic Tool: Scope and Limitations

Alberto Soldevilla, Diego Sampedro,*
Pedro J. Campos, and Miguel A. Rodríguez

Departamento de Química, Universidad de La Rioja, Grupo de Síntesis Química de La Rioja, Unidad Asociada al CSIC, Madre de Dios, 51, E-26006 Logroño, Spain

diego.sampedro@dq.unirioja.es

Received April 29, 2005



The scope and limitations of the photorearrangement of *N*-cyclopropylimines to 1-pyrrolines are presented. The influence on the reactivity of different substituents throughout the cyclopropane ring and at the iminic position of the *N*-cyclopropylimine structure is discussed. The observed effects are interpreted from computational studies. The principal findings relate to (1) the enhanced reactivity of 1-substituted compounds toward rearrangement, (2) the lack of reactivity of crowded cyclopropanes, and (3) the high chemoselectivity of the process.

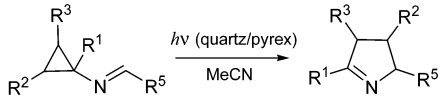
Cyclic imines, and especially 1-pyrrolines, have proven to be valuable intermediates for the synthesis of compounds possessing a wide range of pharmaceutical activities.[1] A variety of syntheses of 1-pyrrolines are available,[1] but only a small number of synthetic routes have found widespread utility. Of these routes, the ring expansion of cyclopropylimines is an attractive and straightforward method. Furthermore, the nature of this reaction chemistry has attracted the attention of theoretical and computational chemists as these systems represent the smallest models for sigmatropic rearrangements and, therefore, lend themselves to be used for high-level calculations.

The initial observation of a cyclopropylimine−pyrroline rearrangement dates from 1929 (the Cloke rearrangement).[2] This reaction, which begins with *C*-cyclopropylimines, was later exploited by Stevens[3] for the synthesis of a number of alkaloids and different five-membered rings that incorporate a nitrogen atom. In this context, it became clear that an acidic catalyst was required to perform the transformation, and therefore, an ionic nature of the rearrangement was indicated.

In contrast, the thermal rearrangement of *N*-cyclopropylimines (in which the iminic nitrogen atom is directly bonded to the cyclopropane ring) was explored for the first time by Huisgen et al. in the 1970s through a study involving 1,3-dipolar cycloadditions.[4] These reactions were limited to a set of very activated compounds (2,2-diphenylcyclopropane derivatives) that underwent rearrangement at moderate temperatures (∼150 °C). Mechanistic studies performed in connection with this reaction indicated the lack of a noticeable solvent effect. Furthermore, the reaction always took place in the absence of a catalyst, suggesting that the opening of the three-membered ring is not accompanied by charge separation in this case. On the basis of this information, involvement of a trimethylene (diradical) intermediate was postulated. In this way, the reaction closely resembled the vinylcyclopropane−cyclopentene thermal rearrangement of the all-*C* system, in contrast to the case of *C*-cyclopropylimines.

We have recently extended the scope of this process through the use of the flash vacuum pyrolysis technique,[5] which permits the rearrangement of a varied set of *N*-cyclopropylimines to occur at ca. 350 °C.

A photochemical version of this type of reaction has been explored to a much lesser extent. The practical applications of the photorearrangement of vinylcyclopropanes are scarce, and most of them deal with strained bicyclic compounds.[6] Indeed, to the best of our knowledge, no papers pertaining to the photoinduced rearrangement of cyclopropylimines had appeared prior to our initial report on the photorearrangement of *N*-cyclopropylimines to 1-pyrrolines[7] (eq 1).



1 **2** (1)

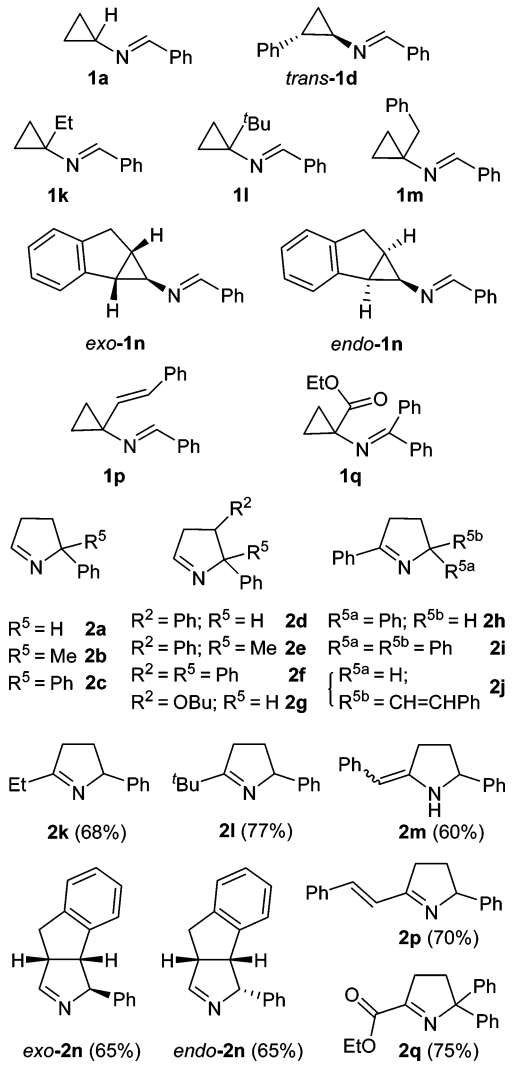
In earlier related work, we studied the mechanism of this process from both an experimental and theoretical point of view,[8] using the simplest model structure of an *N*-cyclopropylimine for the purposes of the calculations. The results obtained in that study and more recent calculations will be discussed here in order to provide a plausible interpretation of observed reaction chemistry.

In our previous work, we explored simple substitution patterns (mainly H- and Ph- groups) on the basic *N*-cyclopropylimine substructure, thus producing compounds **2a**−**j**. In the present study, more complex *N*-cyclopropylimines (**1k**−**r**) were synthesized in an effort to explore and define the scope and limitations of the photoreaction. Pyrrolines **2k**−**q** were thus prepared[9] (isolated yields are shown in parentheses). Considering

(1) Dannhardt, G.; Kiefer, W. *Arch. Pharm. Pharm. Med. Chem.* **2001**, *334*, 183−188.
(2) Cloke, J. B. *J. Am. Chem. Soc.* **1929**, *51*, 1174−1187.
(3) Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193−198.
(4) Caramella, P.; Huisgen, R.; Schmolke, B. *J. Am. Chem. Soc.* **1974**, *96*, 2997−3000.
(5) Campos, P. J.; Soldevilla, A.; Sampedro, D.; Rodríguez, M. A. *Tetrahedron Lett.* **2002**, *43*, 8811−8813.
(6) Sonawane, H. R.; Bellur, N. S.; Kulkarni, D. G.; Ahuja, J. R. *Synlett* **1993**, *12*, 875−884.
(7) Campos, P. J.; Soldevilla, A.; Sampedro, D.; Rodríguez, M. A. *Org. Lett.* **2001**, *3*, 4087−4089.
(8) Sampedro, D.; Soldevilla, A.; Rodríguez, M. A.; Campos, P. J.; Olivucci, M. *J. Am. Chem. Soc.* **2005**, *127*, 441−448.
(9) For the substrate **1m**, with R^1 = benzyl, a secondary photochemical 1,3-hydrogen shift takes place and the isomeric benzylidenepyrrolidine **2m** is finally isolated.

10.1021/jo050871x CCC: $30.25 © 2005 American Chemical Society
Published on Web 07/26/2005

a whole set of substrates, we investigated the influence of different groups attached to the basic structure together with other relevant aspects of the process.



Choice of Reaction Solvent. In our preliminary paper, hexane was used as the reaction solvent. We later found that this solvent is not the best choice and now routinely use acetonitrile. In acetonitrile, the photoreactions tend to be cleaner and less polymeric material is formed, leading to a purer crude product. The solvent effect was studied by measuring the quantity of 1-pyrroline formed and remaining substrate (starting material) present in parallel photoreactions using different solvents. After irradiation, the composition of the mixtures was analyzed by NMR.[10] The observed solvent effect in substrate *trans*-**1d** is summarized in Table 1. The last column gives an indirect estimation of the extent of the polymerization reaction. These results confirm that acetonitrile is indeed a good solvent. Aromatic solvents (toluene, benzene) are also good solvents, but they will absorb incident light when Pyrex light filtering is not used (i.e., in quartz photoreactors). DMSO was also evaluated as a photochemical solvent, and it gave slightly better results than acetonitrile. However, the use of DMSO makes the workup procedure and product isolation more complicated. Other solvents tested tended to give poorer results. There is some correlation between the observed results and solvent polarity.[11] However, the magnitude of the effect was not sufficiently large enough to indicate the involvement of ionic intermediates, and it is more likely to be an indirect effect operating on the polymerization reaction. It should also be noted that typical hydrogen-donor solvents (alcohols, amines, etc.) cannot be used because hydrogen abstraction and subsequent photoreduction take place.[12] After the reaction solvent was changed from hexane to acetonitrile, the observed isolated yields (50−70% for aldimines and 80−95% for ketimines) were similar to the yields reported in the preliminary work, but the use of acetonitrile led to a product requiring less purification, and therefore, this is, practically speaking, a better overall process.

(10) See the Supporting Information of ref 8.

TABLE 1. Solvent Effect in the Photoreaction of *trans*-1d (Irradiation Time: 5 h, Merry-Go-Round Photoreactor)

solvent	yield of 1-pyrroline (%)	unreacted substrate (%)	total (%)
DMSO	48	45	93
MeCN	47	43	90
benzene	54	24	78
toluene	53	23	76
THF	19	52	71
CH_2Cl_2	43	25	68
Et_2O	18	48	66
hexane	17	46	63

Influence of Substitution on the Iminic Carbon (C5). The principal effect observed for the iminic carbon position is related to the influence of the substituents on the rate of photoinduced polymerization of the substrate, which is the principal process leading to a reduction in the chemical yield. Aldimines polymerize more easily, and this leads to moderate chemical yields of 1-pyrroline—lower than those for ketimines, which are more inert toward polymerization. A greater degree of steric hindrance, centered at the iminic carbon in the later case, is a reasonable explanation for this effect. Photopolymerization is a side reaction in this process, and this is also influenced by the reaction solvent, as noted above.

Influence of Groups at C1 of the Cyclopropane. In several cases, it was noted that reaction times were shorter for substrates with a substituent at C1. This observation was investigated by direct comparison of imines **1a**, **1k**, and **1l**, which have increasing steric volume attached to the C1 position (R^1 = H, Et and ^{t}Bu, respectively). These substrates were irradiated in parallel (merry-go-round reactor) in quartz tubes.[10] After 1 h, **2l** had been formed in 62% yield, whereas the yield of **2k** was about 31% and that of **2a** was 25%. The irradiation was prolonged for a further 2 h, and the yield for **2l** rose to 71%, while for **2k** and **2a** it was 52% and 36%, respectively. Finally, **1l** was no longer detected after a further 3 h of irradiation (75% yield of **2l**), while yields of 65% for **2k** and 54% for **2a** were observed. This effect

(11) The best correlation was found for the Taft scale of polarities (Kamlet, M. J.; Abboud, J. L.; Taft, R. W. *J. Am. Chem. Soc.* **1977**, *99*, 6027−6038).

(12) Campos, P. J.; Arranz, J.; Rodríguez, M. A. *Tetrahedron* **2000**, *56*, 7285−7289.

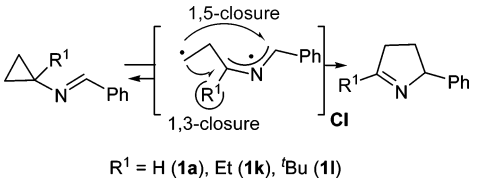


FIGURE 1. Influence of R^1 on the CI structure.

may be understood by taking into account the structure of the conical intersection (CI) for this process (Figure 1). In a photochemical reaction, the CI plays an analogous role to that of the transition state in a thermal process.[13] In this case, the structure of the CI is similar to a diradical (a more or less localized radical at C2 and an aza-allylic delocalized radical along C1NC5). The 1,3-closure of the diradical, which involves the re-formation of the C1−C2 bond of the *N*-cyclopropylimine, represents a path for the deactivation of the excited state (with possible ring isomerization as well). As the volume of the group at C1 increases, this deactivation path is sterically made more difficult compared to the 1,5-closure (through C2−C5 bonding), which leads to the 1-pyrroline product.

Influence of Groups at C2 of the Cyclopropane. Stereoselectivity. The presence of groups on C2 facilitates—through stabilization of a radical—the ring opening and determines the regiochemical outcome of the final 1-pyrroline. Furthermore, such substituents have a direct impact on the stereochemical course of the reactions. We observed a greater level of stereoselectivity in the photoreactions of *trans*-**1d** and *cis*-**1d** when Pyrex-filtered light (λ > 300 nm) was used (~5:1 in both cases, toward the *trans*- and *cis*-pyrroline, respectively),[8] as compared with the corresponding thermal rearrangements[5] (which give practically a 1:1 mixture). It should be noted that, in the present study, analogous behavior was observed for *exo*-**1n** and *endo*-**1n** toward pyrrolines *exo*-**2n** and *endo*-**2n**, respectively, with the same ratio (~5:1) of selectivity as in the case of **1d.**

Influence of Groups at C3 of the Cyclopropane. Reactivity of Crowded Systems. We also explored the reactivity of substrates with substituents attached to all three atoms of the cyclopropane ring. In such crowded cyclopropanes, one might expect deviations from the general reactivity to be common. Vinylcyclopropanes with this type of structure show complex photochemistry, and several compounds apart from cyclopentenes are formed upon irradiation.[14] For example, in the 2-azadi-π-methane reactions which have been reported, *N*-cyclopropylimines with a crowded cyclopropane are formed and remain photostable.[15] There is only one case where rearrangement to the 1-pyrroline has been reported, and this proceeds only in low yields.[15] In our study, we found that bicyclic substrates *trans*-**1n** and *cis*-**1n** form the pyrrolines **2n** according to the general rule.[7] However, in a more crowded system, like **1r**, 1-pyrroline formation was not detected at all even after prolonged irradiation,

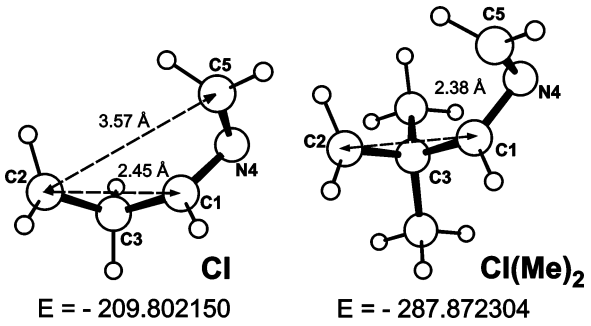
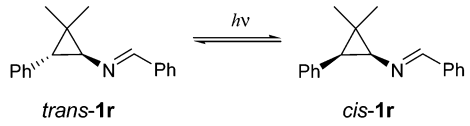


FIGURE 2. Calculated structures for the conical intersection of the model compounds CI and $CI(Me)_2$. Energies are given in hartrees.

and only cis−trans photoisomerization of the cyclopropane ring dominates the reaction (eq 2).



(2)

The reason for this limitation in the rearrangement process, which appears to be more or less a general feature of 3-disubstituted substrates, is not clear, but one can venture a plausible explanation upon analysis of the CI structure (Figures 1 and 2). In a substituent-crowded CI, a "cyclopropane" geometrical disposition of C1, C2, and C3 stabilizes the steric repulsions of the substituents as they are spread throughout the C1C2C3 plane. In contrast, a disposition with distant C2 and C1 atoms, i.e., closer to a five-membered ring geometry, would involve a constriction of the same steric demands within a narrower angle over the C1C2C3 plane. The first situation should be energetically preferred, so C1 and C2 must be closer in the CI point as the initial cyclopropane ring is more crowded with substituents. Such a situation would favor the deactivation path (1,3-closure) as opposed to the pyrroline-formation path. This possibility was also analyzed by calculation of the CI geometry after the introduction of two methyl groups on C3 [CI−$(Me)_2$ from Figure 2]. It was found that the C1−C2 distance shifts from 2.45 to 2.38 Å, which is consistent with the expected effect.

Chemoselectivity. In comparison to the process discussed here, the photorearrangement of the corresponding all-C parent system (vinylcyclopropane) has been established for a long time.[16] The oxa(VCP−CP) rearrangement of cyclopropylcarbonyls has also been described.[17] With the aim of comparing these processes with the *N*-cyclopropylimine rearrangement, we synthesized compounds **1p** and **1q**, both of which contain the appropriate groups (vinyl and imine in **1p**; carbonyl and imine in **1q**) attached to C1 of the cyclopropane ring. Irradiation of **1p** in acetonitrile (3 h, Pyrex filtering) led to the formation of 1-pyrroline **2p** but azadiene **3p** was not detected (Scheme 1). Irradiation of **1p** without a

(13) Robb, M. A.; Garavelli, M.; Olivucci, M.; Bernardi, F. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; Wiley-VCH: 2000; Vol. 15, Chapter 2.

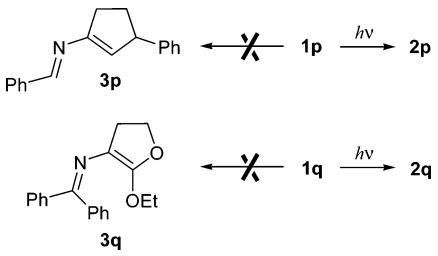
(14) Zimmerman, H. E.; Oaks, F. L.; Campos, P. *J. Am. Chem. Soc.* **1989**, *111*, 1007−1018.

(15) Armesto, D.; Caballero, O.; Ortiz, M. J.; Agarrabeitia, A. R.; Martín-Fontecha, M.; Torres, R. *J. Org. Chem.* **2003**, *68*, 6661−6671.

(16) Baldwin, J. E. *Chem. Rev.* **2003**, *103*, 1197−1212.

(17) (a) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165−198. (b) Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 899.

SCHEME 1. Chemoselectivity of the Rearrangement of 1p and 1q



Pyrex filter (quartz reactor) produced the same result. Similarly, irradiation of **1q** only afforded **2q** as a photoproduct (in this case the UV light must not be filtered).

These examples demonstrate the high chemoselectivity of the rearrangement involving the imine moiety. However, irradiation of several *C*-cyclopropylimines (with an inverse attachment of the imine to the cyclopropane) was also explored and in all cases pyrrolines were not obtained. After several hours of irradiation, only polymeric material was recovered. The 1-aza-di-π-methane rearrangement[18] is reported to give *C*-cyclopropylimines that do not rearrange to 1-pyrrolines. These observations suggest that the precise orbital structure of the unsaturated group is a determinant for the process. However, steric factors could also be relevant.

In conclusion, a general framework for the use of the *N*-cyclopropylimine-1-pyrroline photorearrangement as a tool in organic synthesis has been outlined. This reaction provides a new, simple, and straightforward method for the preparation of substituted 1-pyrrolines.

Experimental Section

General Procedure for the Synthesis of Benzaldimines. Synthesis of 1-Ethyl-*N*-[(1*E*)-phenylmethylene]cyclopropanamine (1k). Benzaldehyde (1 mmol) was added to a solution of 1-ethylcyclopropanamine (1 mmol) in CH_2Cl_2 (20 mL). Molecular sieves were added (3 Å, ca. 1 g), and the mixture was stirred at rt for 2 h. The solution was filtered and the solvent evaporated in vacuo to give **1k** (96% yield): ^{1}H NMR ($CDCl_3$) δ 0.75−0.82 (m, 2H), 0.94−0.99 (m, 2H), 0.96 (t, 3H), 1.80 (q, 2H), 7.36−7.40 (m, 3H), 7.69−7.74 (m, 2H), 8.22 (s, 1H); ^{13}C NMR + DEPT ($CDCl_3$) δ 10.5 (CH_3), 14.3 (CH_2), 29.1 (CH_2), 47.8 (quaternary C), 127.8, 128.5, 130.2 (aromatic CH), 136.7 (aromatic quaternary C), 157.1; *m/z* (EI^+) 173 (25, M^+), 158 (40), 145 (46), 144 (89), 130 (49), 118 (41), 117 (100), 116 (14), 104 (16), 103 (15); *m/z* (ES^+) 174 (M + 1). Anal. Calcd: C, 83.19; H, 8.73; N, 8.08. Found: C, 83.16; H, 8.75; N, 8.05.

(18) Armesto, D. In *CRC Handbook of Organic Photochemistry and Photobiology*; Horspool, W. M., Song, P.-S., Eds.; CRC Press: 1995; Chapter 73, pp 915−936.

Synthesis of *N*-(Diphenylmethylene)-1-ethoxycarbonylcyclopropanamine (1q). Benzophenone imine (1 mmol) was added to a solution of 1-ethoxycarbonylcyclopropanamine (1.1 mmol) in dry toluene (20 mL). Molecular sieves were added (3 Å, ca. 1 g), and the mixture was stirred at 80 °C for 24 h. The solution was filtered and the solvent evaporated in vacuo. The product was purified by flash column chromatography on silica gel, using a 9:1 mixture of hexane/ethyl acetate as eluent, to give **1q** (90% yield). Alternatively, a room-temperature condensation method[19] can also be used, and this gives a similar yield. Both methods can be generally used for the syntheses of benzophenone imines from cyclopropylamines: ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 3H), 1.16−1.20 (m, 2H), 1.46−1.50 (m, 2H), 3.92 (q, 2H), 7.22−7.42 (m, 8H), 7.60−7.63 (m, 2H); ^{13}C NMR + DEPT ($CDCl_3$) δ 14.0 (CH_3), 20.3 (CH_2), 45.3 (quaternary C), 60.8 (O-CH_2), 127.9, 128.2, 128.3, 128.9, 130.0, 130.4 (aromatic CH), 137.8, 140.0 (aromatic quaternary C), 172.4, 174.2; *m/z* (EI^+) 293 (6, M), 220 (22), 219 (17), 192 (22), 166 (34), 165 (100), 117 (14), 115 (16); *m/z* (ES^+) 294 (M + 1). Anal. Calcd: C, 77.79; H, 6.53; N, 4.77; O, 10.91. Found: C, 77.82; H, 6.55; N, 4.76.

General Procedure for the Synthesis of 1-Pyrrolines. Photolysis of 1k. A solution of **1k** (1 mmol) in dry acetonitrile (50 mL) was placed in an immersion-well quartz photoreactor equipped with a 125 W medium-pressure mercury lamp. The system was purged with argon for 15 min and irradiated for ca. 2 h. When the substrate was consumed (determined by TLC), the solution was filtered and the solvent evaporated. The crude product was purified by flash column chromatography on silica gel, using an 8:2 mixture of hexane/ethyl acetate as eluent, to give 1-ethyl-2-phenyl-3,4-dihydro-2*H*-pyrrole **2k** (68% yield). Analytical samples were obtained by vacuum distillation ((9−10) $\times 10^{-3}$ Torr, 70 °C): ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3H), 1.64−1.78 (m, 1H), 2.39−2.48 (m, 1H), 2.45 (q, 2H), 2.50−2.62 (m, 1H), 2.58−2.72 (m, 1H), 5.03−5.10 (m, 1H), 7.18−7.32 (m, 5H); ^{13}C NMR + DEPT ($CDCl_3$) δ 8.0 (CH_3), 28.6 (CH_2), 35.5 (CH_2), 37.7 (CH_2), 75.5 (CH), 126.5, 126.7, 128.4 (aromatic CH), 144.8 (aromatic quaternary C), 180.2; *m/z* (EI^+) 173 (93, M^+), 172 (10), 158 (41), 145 (44), 144 (68), 130 (31), 118 (38), 117 (100), 116 (11), 115 (19), 104 (15), 103 (11); *m/z* (ES^+) 174 (M + 1). Anal. Calcd: C, 83.19; H, 8.73; N, 8.08. Found: C, 83.15; H, 8.76; N, 8.10.

Acknowledgment. We thank the Spanish MCyT (BQU2001-1625), the Universidad de La Rioja (API-04/06), and the Comunidad Autónoma de La Rioja (ACPI-2003/08) for financial support. A.S. thanks the Spanish MEC for his grant. D.S. is financed by the Ramón y Cajal program from the MEC.

Supporting Information Available: Complete experimental procedures, references for known compounds, characterization data for new compounds, computational details, and Cartesian coordinates for calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050871X

(19) O'Donell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663−2666.