Tetrahedron 67 (2011) 7570–7574

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Photochemical characterization of biomimetic molecular switches

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ARTICLE INFO

Article history:
Received 29 June 2011
Accepted 21 July 2011
Available online 28 July 2011

Keywords:
Molecular switches
Photochemistry
Photoisomerization
Sigmatropic rearrangement
Retinal

ABSTRACT

The performance of fluorenylidene–pyrroline (FPs) and *N*-alkylated fluorenylidene–pyrroline (NAFPs) derivatives for their use as light-driven molecular switches has been studied. Both types of compounds share fast and controllable photoisomerization. Other competitive reaction pathways that could lead to low efficiency have been considered. Only weak fluorescence was measured and high photostability was found when irradiating these compounds for long times, together with high photoisomerization quantum yields. NAFPs are capable of using visible light, which could be useful for practical applications.

1. Introduction

The synthesis and applications of molecular switches based on photochemical *E*/*Z* isomerizations have received much attention in recent years.[1,2] Among this type of compounds, azobenzene derivatives have been extensively used for very different uses in several contexts to convert light energy into 'mechanical' motion at the molecular level.[3,4] Thus, azobenzene-based switches have been employed to control ion complexation,[5] to modify electronic properties,[6] or to trigger folding/unfolding of oligopeptides[7,8] and other biological applications.[9,10] Although, their unique properties as effective switches, azobenzene derivatives are just one type of compounds capable of performing controlled *E*/*Z* isomerization. Consequently, the preparation and characterization of novel switches that differ from azobenzene in properties, such as size, polarity and isomerization mechanism represents an attractive research target. The discovery of new or alternative building blocks could expand the applicability of the switch concept to different and increasingly complex molecular environments. A use of the above principle led to the preparation of chiral diarylidenes, featuring a single isomerizable C=C bond. These systems afford light-driven molecular rotation along the central double bond and the chiral framework imposes a preferential direction of isomerization.[11,12]

One of the most remarkable examples in Nature of a molecular motor is the retinal chromophore of rhodopsin (Rh), which suffers a *cis–trans* photoisomerization during the process of vision.[13] Rh is a photoreceptor protein (a visual pigment), which is located in the rod visual cells responsible for twilight vision. Rh has 11-*cis* retinal as its chromophore, which is embedded inside a single peptide transmembrane protein called opsin. In Rh a selective photoisomerization of the 11-*cis* chromophore (PSB11) occurs via evolution of a single $\pi \rightarrow \pi^*$ excited state (S_1) that survives for only 150 fs and yields, upon decay, the all-trans ground state (S_0) product with a 67% quantum yield.[14] These properties make Rh an excellent starting point for the design of *E*/*Z* switches. However it should be noted that irradiation of PSB11 in solution features an unselective isomerization and a picosecond excited state lifetime.[14] Thus, the search for artificial Rh-mimetic molecules capable of maintaining similar properties in solution seems an attractive research target. In this context, theoretical calculations can also be helpful in order to get some insight into the features needed for efficient switches based on the PSB11.[15]

Using this strategy, it has been recently reported the synthesis[16] of an *N*-alkylated indanylidene–pyrroline (NAIP, Fig. 1) Schiff base that displays, in methanol solution, excited state properties similar to those of Rh-embedded PSB11.[17] These switches display absorption maxima in the near-UV region. Clearly, the design and synthesis of switches capable of absorbing in the visible constitute a major target. Bearing this idea in mind we designed a new type of switch based in the PSB11 where the indanylidene unit of NAIPs was replaced for moieties displaying a more expanded π-system. Specifically, we focused on switches where the indanylidene unit has been replaced by a fluorenylidene unit. Through the preparation of a library of fluorenylidene–pyrroline (FPs) and *N*-alkylated fluorenylidene–pyrroline switches (NAFPs, Fig. 1), we showed that it is possible to obtain biomimetic light-driven switches where the

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doi:10.1016/j.tet.2011.07.070

absorption maximum of the unsubstituted system was red-shifted by >50 nm with respect to that of the NAIPs. We also showed that, as it happened with NAIP switches, FPs and NAFPs undergo $Z \rightarrow E$ and $E \rightarrow Z$ photoisomerization displaying a photomodulable stationary state.[18,19]

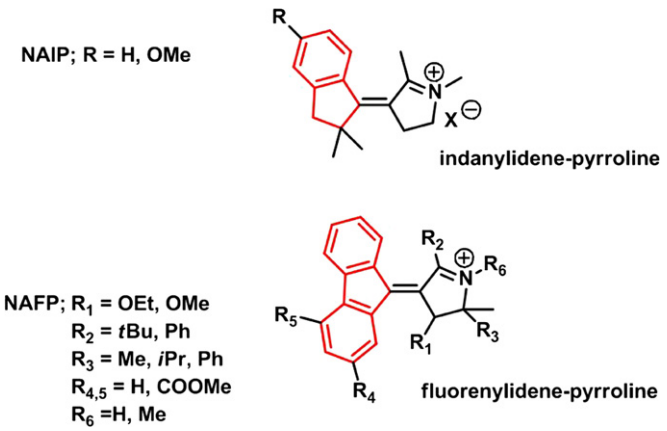


Fig. 1. NAIP and NAFP switches.

In our previous study,[18] we proposed the use of FPs and NAFPs as potentially practical molecular switches. We also compared the performance of both types of compounds. Thus, NAFPs feature a strong absorption in the visible that make them quite useful when low-energy irradiation is needed. Due to this, clean and cheap sunlight could be used as the energy source. Even more, photoisomerization of NAFPs is four times faster than FPs. Although NAFPs present some promising features, a complete study of the photochemical behavior is necessary before more complex applications could be envisaged. This is especially important in the case of a new molecular switch, but it should be noted that in many cases different compounds are proposed and used as molecular switches without a complete understanding of the competitive pathways hindering their role as effective switches. Before a certain compound could be defined and used as a good molecular switch, one should be aware of different processes that could lead to a decrease in the efficiency. Thus, it is important not only to determine the switching capacity of new compounds, but also to quantitatively establish the relevance of other processes that could eventually lead to a poor performance as a molecular switch. For instance, luminescence, low quantum yields of isomerization, slow isomerization, low photostability or side-reactions yielding by-products could turn a promising candidate into a compound without practical use. Thus, herein we report our study on the competitive processes that could thwart the practical uses of FPs and NAFPs.

The *E*/*Z* isomerization process for FP and NAFP derivatives has been previously reported.[18] The progress of the photoreaction starting from pure samples of any isomer can be easily followed by ^{1}H NMR to yield equivalent mixtures (see Supplementary data). The competitive thermal isomerization takes place in a much longer time scale (more than 15 h at 50 °C). Several competitive pathways were explored in order to decide the proficiency of FPs and NAFPs as molecular switches. First, an efficient luminescent deactivation was considered. If fluorescence or phosphorescence is quantitatively important, only a fraction of the molecules will be able to use the light energy to isomerize. In second place, photostability of FPs and NAFPs was checked by irradiating the samples well beyond the photostationary state. Also, as a measure of the efficiency of the switching process, the isomerization quantum yield at low conversions was measured. Finally, the effect of different wavelengths in the switching process was checked.

2. Results

2.1. Excited state multiplicity

Our first step was to determine the nature of the excited state involved in the photoisomerization. This is relevant not only to explore alternative reactive pathways, but also to study the luminescence of these compounds. In order to do this, several runs of an experiment with three different samples of a solution of an FP switch were performed. The samples in every run were irradiated at the same time using a merry-go-round photochemical reactor (see Experimental section for details). A solution of **1** (R_1=EtO, R_2=Ph, R_3=Me, R_4=CO_2Me, R_5=H, Fig. 2) in acetonitrile was used as blank, while two more solutions were prepared with oxygen-saturated solvent and 5 equiv of *cis*-piperylene, respectively, as triplet quenchers. After irradiating for 5 min all three samples for every run afforded the same mixture of isomers composed by 77±1% of the starting isomer **1** and 23±1% of the photoisomer **1′**. Thus, in all three cases, including the samples containing triplet quenchers, the photoisomerization proceeded equally. This suggests an excited state of singlet nature. This is not surprising due to the fact that the photoisomerization of the model reference for the design of NAFP switches, the PSB11, also takes place in the singlet potential energy surface, as it happens with related compounds.[20]

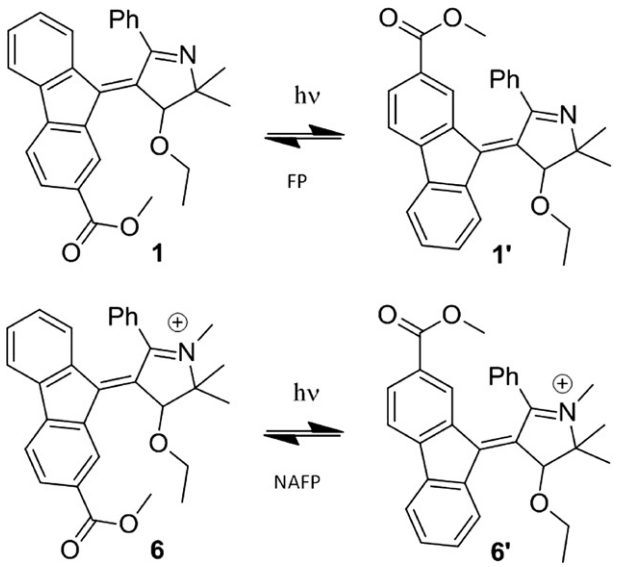


Fig. 2. Photochemical isomerization of FP and NAFP switches.

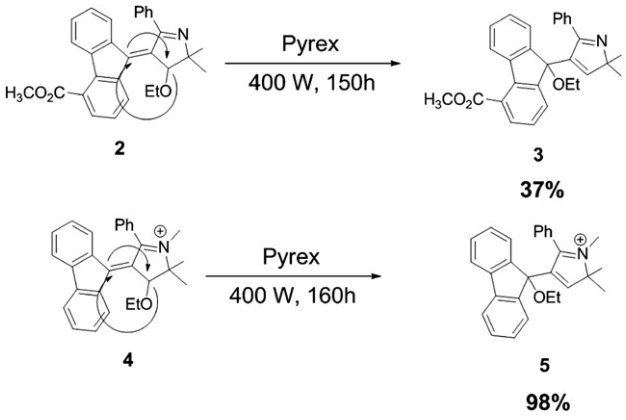
2.2. Fluorescence measurements

Once assessed the nature of the excited state involved in the photoisomerization, we aimed for the study of deactivation processes that could diminish the efficiency of the FP switches. We measured the emission and excitation spectra of a 3×10^{-5} M solution of **1** in deoxygenated acetonitrile at 298 K. Only a weak emission band centered at 430 nm was obtained when exciting from 270 nm to 350 nm (see Experimental section for details). The fluorescence lifetime was found to be 4.30×10^{-9} s. In order to determine the fluorescence quantum yield, a solution of *trans*-stilbene in deoxygenated hexane was used as standard of fluorescence. A solution of **1** in deoxygenated acetonitrile was also prepared and the emission spectra for both compounds were measured using an excitation wavelength of 290 nm. Under these conditions, a fluorescence quantum yield of 0.06 (±0.02) was found. This value shows that deactivation through fluorescence does not effectively compete with the isomerization process. In fact, this result

emphasizes the adequate design of these switches as only a small fraction of the light energy is wasted in the radiative decay.

2.3. Photostability

Next, we explored the photostability of FPs and NAFPs. In order to be useful, compounds acting as switches should be photostable so as to allow as many photocycles as possible to take place. Thus, we checked the photostability of these compounds by irradiating them well beyond the photostationary state. Although in a typical photoisomerization (see Experimental section for details) the photostationary state is reached within 0.5 h using a 125 W medium-pressure Hg lamp, after irradiating **2** (R_1=EtO, R_2=Ph, R_3=Me, R_4=H, R_5=CO_2Me, Scheme 1) for 100 h, no decomposition was observed by ^{1}H NMR, as only the two isomers could be detected. Thus, FPs showed again good features as switches for practical applications. With the aim of checking the limits of the photoisomerization, we irradiated even longer periods of time using a 400 W medium-pressure Hg lamp. After more than 150 h, new signals were found in the ^{1}H NMR spectrum. This new compound could be characterized as **3** (Scheme 1).



Scheme 1. Rearrangement of **2** and **4** to yield **3** and **5**.

Formation of **3** can be explained by a photochemically allowed [1,3]sigmatropic rearrangement. Although this reaction clearly does not affect the use of FPs as switches due to the different time scale of the two processes (0.5 h with a 125 W lamp vs more than 150 h with a 400 W lamp) it could be of some interest in other context. Thus, we also checked the photostability of NAFPs by irradiating **4** (R_1=EtO, R_2=Ph, R_3=Me, R_4=H, R_5=H, R_6=Me, Scheme 1) for long times using a 400 W Hg lamp. After ca. 160 h compound **5**, the rearranged product analogue to **3**, was also found and, in this case, it could be obtained in 98% after recrystallization. Thus, as it has been seen in the preliminary studies of FPs and NAFPs,[18] the methylated analogues react faster. This transformation presents no practical use as it takes place in these compounds, due to the long irradiation times needed to yield the rearranged products. In fact, the systems were designed to minimize competitive reactions. However, the same methodology could be used for the synthesis of pyrrole derivatives using compounds where the energy could be effectively employed in the rearrangement. For instance, analogues of **5** have been recently used in the synthesis of merocyanine dyes,[21] act as direct precursors of stable cyclic alkylaminocarbenes[22] and take part on the structure of certain alkaloids,[23] just to mention some applications. However, regarding the photoisomerization process of FPs and NAFPs, this rearrangement could be considered negligible as both types of compounds present considerable photostability. The process shown in Scheme 1 could be due to photochromism, either type P or T. In order to check this, we irradiated a pure sample of **5** with a medium-pressure Hg lamp and without a Pyrex filter. Compound **5** has a band maximum located at 270 nm (Fig. 3). However, no back-reaction was found and **4** could not be detected in the reaction crude. We also checked the thermal back-reaction by heating **5** in refluxing toluene for 2 days. Again, formation of **4** was not detected and **5** could be recovered unaltered. Thus, formation of **3** and **5** is not reversible and it could be used to synthesize pyrrole derivatives using more adequate substrates.

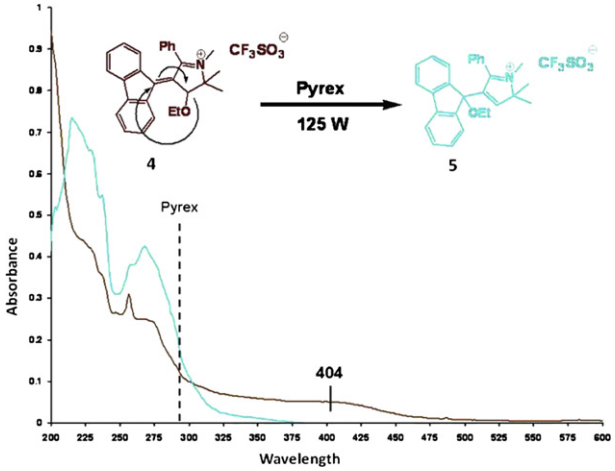


Fig. 3. UV spectra for **4** and **5**.

2.4. Isomerization quantum yield

Once studied the competitive pathways that could decrease the competence for the switching process in FPs and NAFPs, we aimed for a direct measurement of their efficiency. Thus, we evaluated the isomerization quantum yield of **1** (FP) and **6** (NAFP, R_1=EtO, R_2=Ph, R_3=Me, R_4=CO_2Me, R_5=H, R_6=Me, Fig. 2) using *trans*-azobenzene as actinometer (see Experimental section for details). For the FP **1**, we obtained an average value of 0.6 (±0.1) after several runs. For the NAFP **6** a value of 0.5(±0.1) was found. It should be noted that these values for the quantum yield are comparable to those found for the PSB11 in vivo (0.67 for Rh)[13,14] and bigger than those reported for biarylidenes (0.07–0.55).[11] Thus, both FPs and NAFPs can efficiently use the light energy into the switching process and show very promising features for their use in practical applications.

2.5. Photostationary state composition

In order to further evaluate the potential use of these compounds, we explored the effect different experimental conditions could cause in the photostationary state (PSS). Once assessed the lack of competitive reaction paths, the use of FPs and NAFPs as switches could be affected by the experimental conditions. Specifically, the composition of the photostationary state is relevant when it comes to practical applications as it will determine the macroscopic modification induced for the switch once incorporated in a complex system. For FPs the photostationary state is composed by a mixture of ca. 45:55 (**1**:**1**′) as shown by the value found for **1** (see Experimental section for details, Table 1).

Table 1
Photostationary states and thermal equilibria for FPs and NAFPs

	1 (FP)	**6** (NAFP)
hν	45:55	57:43
Δ	62:38	59:41

Interestingly, in the analogue NAFP the main isomer found in the PSS is different with a mixture of 57:43 (**6**:**6′**) (Table 1). Also, the equilibrium between isomers **1** and **1′** can be displaced from the PSS after heating at 50 °C for several hours. Thus, the main isomer can be easily modified by choosing between light and heat. However, in the case of the mixture of **6** and **6′**, the composition remains almost unaltered. In this case, FPs show a more versatile behavior than NAFPs as different stimuli can afford a different main component of the mixture. This could be important in practical applications in which on/off switching cycles are necessary.

We also checked the effect of the solvent in the PSS. Irradiation on both FP **1** and NAFP **6** in acetonitrile and chloroform slightly affected the relative rate constants[18] but the PSS remained the same within the experimental error. Finally, we explored the wavelength dependence in the photoisomerization of **6**. This factor could allow for an easy and fast change in the PSS under a very simple modification in the reaction conditions. Using a monochromatic light, we followed the photoisomerization process at 330 and 433 nm (see Experimental section for details). We chose those wavelengths because they have the same extinction coefficient (ε=1060) at both sides of the absorption band maximum. Under these conditions, solutions of the same concentration will absorb exactly the same amount of light. We found again the same composition of the PSS (57% of **6** and 43% of **6′**) for the irradiation at these two wavelengths for 6 h. This is not surprising as **6** and **6′** have almost identical UV spectra and are almost equally stable. However, this fact emphasizes the usefulness of these compounds under low-energy irradiation, as the use of quite long wavelengths affords the same results than isomerization under more energetic conditions.

3. Conclusions

The design of molecular devices capable of performing controllable movements can be done using natural molecules as models. In this case the rhodopsin chromophore inspired the design of two types of molecular switches. Fluorenylidene–pyrroline (FPs) and *N*-alkylated fluorenylidene–pyrroline (NAFPs) derivatives show promising features for their use as light-driven molecular switches. Both types of compounds share some characteristics that make them capable of practical applications. Not only show fast and controllable photoisomerization, but also other competitive reaction pathways than could lead to low efficiency are at a minimum. Only very weak fluorescence was measured and high photostability was found when irradiating these compounds for long times. Thus, light energy is mainly used in the photoisomerization process, which takes place with a quantum yield higher than related compounds and comparable to those found in the PSB11 in vivo. Although both FPs and NAFPs share most of the advantages, they also differ in some features. For FPs the photostationary state can be only slightly affected by the reaction conditions, but using heat as the external stimuli the main isomer found in the equilibrium is different. NAFPs share the same ratios of ca. 1:1 when both heat and light are used as stimulus. This is probably the main drawback of these switches as these values would prevent complete exploitation of energy. Still, these values can be modified once the switches are included in a more complex system. However, NAFPs are capable of using low-energy visible light, which could be very useful for practical applications in the presence of a complex matrix and sunlight exploitation.

4. Experimental section

4.1. General experimental methods

All commercially available materials were used without further purification. NMR spectra were recorded on a 300 or 400 MHz NMR spectrometer. ^{1}H NMR samples were internally referenced to TMS (0.00 ppm). 125 W or 400 W medium-pressure Hg lamps were used for the photoisomerization. The synthesis of **1**, **2**, **4**, and **6** has been already reported.[18]

4.2. Typical procedure for the irradiation

A solution for each compound was prepared and irradiated at room temperature under Ar atmosphere through Pyrex glass with a medium pressure-mercury lamp (125 W). The isomerization reaction was followed by ^{1}H NMR.

4.3. Excited state multiplicity

Three different solutions 0.005 M of **1** in acetonitrile were irradiated in quartz tubes with a medium-pressure Hg lamp using a merry-go-round reactor. One of the solutions was used as a blank. In the other two, a triplet quencher was added. In one case the solvent was saturated with O_2 by bubbling for 15 min. In the other case, 5 equiv of *cis*-piperylene were added. The three solutions were irradiated at the same time for 5 min. After that, the product composition was analyzed by ^{1}H NMR. Several runs were performed to ensure experimental liability.

4.4. Fluorescence measurements

Luminescence spectra, fluorescence lifetime and fluorescence quantum yield were recorded at room temperature with a spectrofluorimeter and lifetime data were fitted using the spectrofluorimeter software. Quartz cuvettes (1.0 cm path length) were used for the measurements. In order to determine the fluorescence quantum yield, a solution of *trans*-stilbene in deoxygenated hexane was used as standard of fluorescence. A solution of **1** in deoxygenated acetonitrile was used for the fluorescence lifetime and quantum yield measurements see Supplementary data for spectra. In the last case, a solution of *trans*-stilbene in hexane was used as standard as its absorption and emission spectra are similar to **1**.[24] The emission spectra for both compounds were measured using an excitation wavelength of 290 nm.

4.5. Isomerization quantum yield

The photoisomerization quantum yield for **1** and **6** was measured using *trans*-azobenzene as actinometer.[25] A solution of the FP or NAFP in acetonitrile was prepared in such a way that the absorption a 313 nm was the same for both solutions. Irradiation at 313 nm was performed using a monochromator with a 500 W Hg arc lamp placed in a proper lamp housing, being the samples placed in quartz cuvettes (1.0 cm path length). Solutions of the actinometer were irradiated before and after the irradiation of the switches to ensure the stability of the light source. Due to the short irradiation times of this experiment, thermal isomerization of compounds **1** and **6** was not considered as thermal isomerization requires heating for longer times. Quantification of the samples was performed by ^{1}H-NMR using 1,3,5-trimethoxybenzene as standard.

4.6. Photostationary state composition

To measure the PSS at different wavelengths, solutions of **1** and **6** in different solvents were converted to **1**/**1′** or **6**/**6′** mixtures using monochromatic light until no change in composition was observed by ^{1}H NMR. A 500 W Hg (Xe) lamp was used as light source. A water filter was used to remove infrared radiation and wavelength was selected with a monochromator.

4.7. Synthesis of 3 and 5

A solution of **2** or **4** was prepared and irradiated at room temperature under Ar atmosphere through Pyrex glass with a medium pressure-mercury lamp (400 W) for ca. 150 h. The reaction was followed by ^{1}H NMR and TLC until consumption of the starting material. Compound **3** is obtained as an inseparable mixture. All attempts to purify it by column chromatography failed. Characterization was made by comparison of its spectroscopical data with those of **5**, but results from GC/MS and HRMS could be obtained from the crude. GC/MS: 438 (M+1, 10), 323 (20), 104 (100). HRMS ($C_{29}H_{28}NO_3$) calculated 438.2069, obtained 438.2064 In the case of **5**, the reaction proceeds almost quantitatively. The product can be obtained completely pure as an orange solid by recrystallization from acetonitrile/toluene (1:1) at room temperature. ^{1}H NMR (400 MHz, CD_3CN): δ 8.48–8.47 (m, 1H), 7.39–7.21 (m, 9H), 6.91–6.89 (m, 2H), 6.13–6.12 (m, 2H), 3.09–3.07 (m, 3H), 2.82 (q, J=6.97, 6.94, 6.94 Hz, 1H), 1.94 (dd, J=4.81, 2.40 Hz, 1H), 1.73 (s, 3H), 1.71 (s, 3H), 1.20–0.88 (m, 3H) ppm. ^{13}C NMR (400 MHz, CD_3CN): δ 179.0, 161.7, 146.4, 143.3, 143.0, 142.6, 142.4, 141.2, 131.1, 130.8, 129.2, 129.1, 128.8, 128.7, 126.5, 126.4, 125.9, 125.5, 121.3, 121.2, 118.2, 84.6, 79.6, 58.9, 33.6, 33.5, 21.2, 15.5 ppm. UV–vis (acetonitrile): λ 222 nm (ε=21823 M^{-1} cm^{-1}), λ 279 nm (ε=11096 M^{-1} cm^{-1}). HRMS ($C_{30}H_{30}NO_3$) calculated 452.2220, obtained 452.2228. Melting point (uncorrected) 157–159 °C.

Acknowledgements

We thank the Spanish MEC (CTQ2007-64197) for financial support. L.R.-C. thanks the Comunidad Autónoma de La Rioja for her fellowship. M.B.-L. thanks the Spanish MEC for her grant.

Supplementary data

^{1}H and ^{13}C NMR spectra, UV spectra and GC/MS data for **1**, **3**, **5**, and **6**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.070.

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