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Regiospecific photoisomerization of fluorinated (*E*,*E*)-1,4-diphenyl-1,3-butadienes

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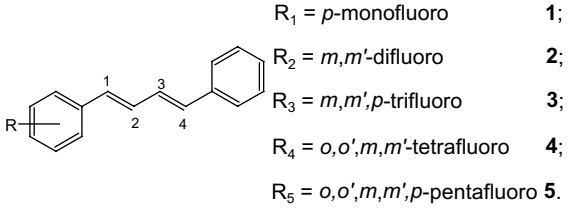
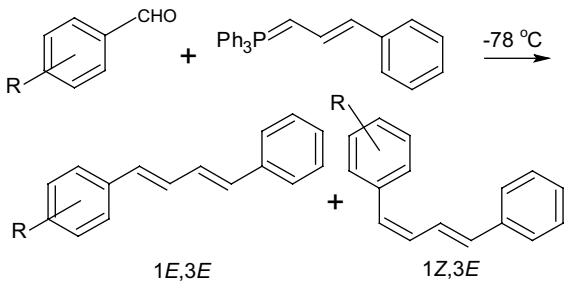
Abstract—Photoisomerization of five fluorinated *E*,*E*-1-(R-phenyl)-4-phenyl-1,3-butadienes in solution (R = **1**: *p*-monofluoro, **2**: *m*,*m*′-difluoro, **3**: *m*,*m*′,*p*-trifluoro, **4**: *o*,*o*′,*m*,*m*′-tetrafluoro, **5**: *o*,*o*′,*m*,*m*′,*p*-pentafluoro) was investigated via direct irradiation. Our results indicated that cis–trans photoisomerization of the fluorinated 1,4-diphenyl-1,3-butadienes in the excited singlet state took place exclusively at the C=C bonds closer to the fluorine substituents.

Cis–trans photoisomerization has been known as the trigger for signal generation by natural visual pigments.[1] During the past decades, many studies have been devoted to understanding the complicated natures of these natural pigments in the excited states, due to their pivotal importance to visual systems.[2] In an attempt to better understand the regiospecificity of photoisomerization of retinal and other natural pigments, photoisomerization of short polyenes in the excited singlet state as model systems has been investigated experimentally as well as theoretically.[3–5] Although photochemical properties of the parent 1,4-diphenyl-1,3-butadiene have been well elucidated,[6] a few studies of regioselectivity of photoisomerization of 1,4-diphenyl-1,3-butadienes were reported.[7] Recently, the unexpected regioselectivity, favoring isomerization at one carbon center of symmetric 1,4-diphenyl-1,3-butadienes via a Hula–Twist process, was observed in organic glass at liquid nitrogen temperature.[8] However, it is still unclear whether the regioselectivity of photoisomerization of unsymmetric 1,4-diphenyl-1,3-butadienes can be demonstrated in solution. Our results from an earlier study showed the regioselective photoisomerization of *cisoid* fluorinated 1,4-diphenyl-1,3-butadienes.[9] Hence, it has occurred to us that in order to reveal the critical factors that determine the selectivity of photoisomerization of linear 1,4-diphenyl-1,3-butadienes, systematical study of fluorine effects on photoisomerization in the excited singlet state is necessary. In this regard, we investigated the electron-withdrawing effect on the regioselectivity of photoisomerization of five fluorinated 1,4-diphenyl-1,3-butadienes (DPB, **1**–**5**).



To synthesize the (1*E*,3*E*) isomers, the substituted benzaldehydes were reacted with cinnamylidenetriphenylphosphorane at 0 °C, respectively (Scheme 1), to yield



Scheme 1.

Keywords: Photoisomerization; Excited singlet state; DPB.
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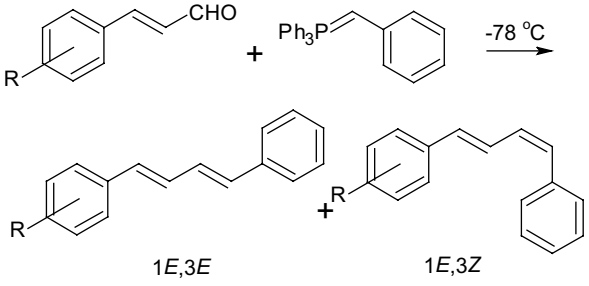
crude products in 60–70% yield. Each crude mixture was further separated by silica gel column chromatography (0–5% ethyl acetate in hexane as an eluant) to afford the (1*E*,3*E*) and (1*Z*,3*E*) isomers in a ratio of ~3:2. To unequivocally distinguish the (1*Z*,3*E*) isomers **1**–**5** from the corresponding (1*E*,3*Z*) isomers that could possibly be formed from photoisomerization in a minute yield, we prepared the five (1*E*,3*Z*) isomers of **1**–**5**. Synthesis of the (1*E*,3*Z*) isomers was accomplished in two steps. First, the substituted *E*-cinnamaldehydes were prepared by C_2-extension of the substituted benzaldehydes with (triphenylphosphoranylidene)acetaldehyde, respectively. Then, the fluorinated *E*-cinnamaldehydes were coupled with benzyltriphenylphosphonium bromide using sodium bis(trimethylsilyl)amide as a base at −78 °C, respectively, to afford crude products containing the major (1*E*,3*Z*) isomers plus the (1*E*,3*E*) isomers in an overall yield of 85–90% (Scheme 2). Two *E*/*Z* isomers were further separated by using the same chromatographic conditions. All the synthetic DPBs were characterized by spectroscopic methods (see Supplementary data). In Figure 1, UV absorption band of the (1*E*,3*E*) isomer (**5**) is shown to have a fine structure, which is characteristic of UV absorption bands of all the (1*E*,3*E*) isomers.[15] Also, the cis bands have been noticed in the UV–vis absorption spectra of all the (1*E*,3*Z*) and (1*Z*,3*E*) isomers (**1**–**5**) (see Supplementary data).

Direct irradiation of the (1*E*,3*E*)-isomer (**5**) in chloroform-*d* (0.015–0.002 M) was carried out using a 200 W Hg medium-pressure lamp with a Pyrex filter ($\lambda > 300$ nm). At the beginning of 14 min, the progress of the reaction was monitored by ^{1}H NMR and HPLC every 2 min, and then the photoreaction was checked every 15 min until it reached a photostationary state. During the irradiation course, it was found that the (1*E*,3*E*)-isomer was isomerized to yield the (1*Z*,3*E*) isomer (Fig. 2). On the other hand, the proton absorption (dd) at δ 7.64, which was assigned to H-2 of the (1*E*,3*Z*) isomer, was undetected indicating that the (1*E*,3*Z*) isomer was not formed from photoisomerization (Figs. 3 and 4). After irradiation, the remaining (1*E*,3*E*)-isomer in the mixture was isolated by silica gel column chroma-



Scheme 2.

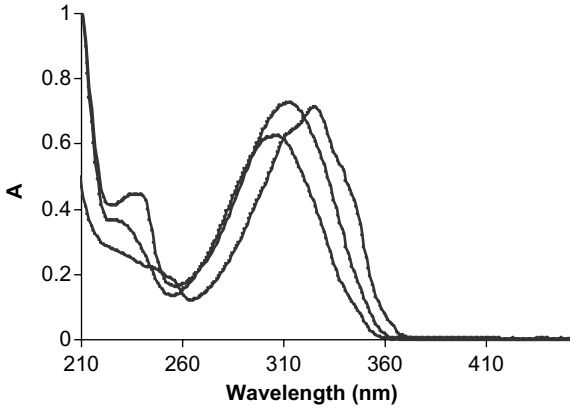


Figure 1. UV Absorption maxima of the (1*E*,3*E*), (1*Z*,3*E*), and (1*E*,3*Z*) isomers (**5**) in hexanes are 326, 307, and 312 nm, respectively. The concentrations are varied.

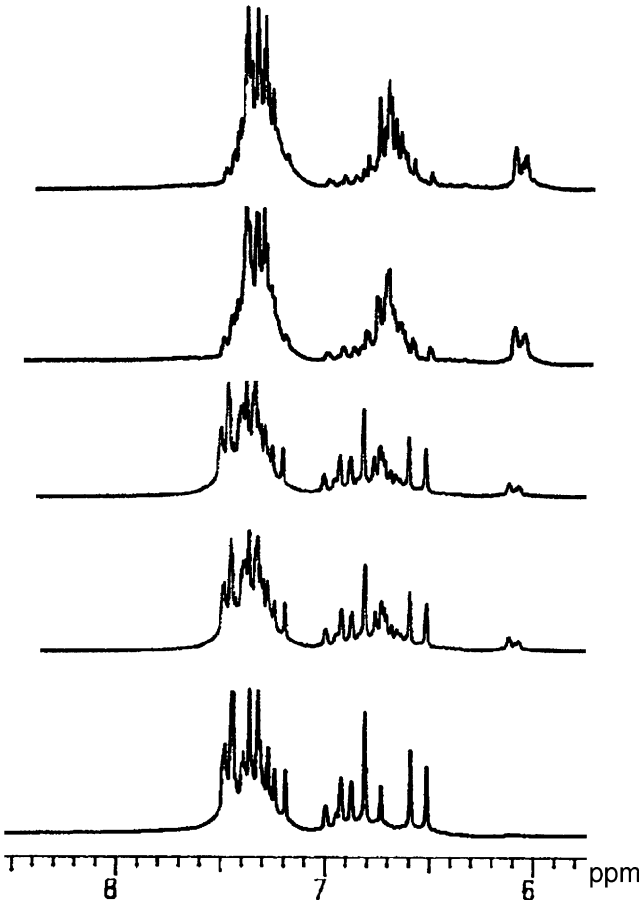


Figure 2. ^{1}H NMR spectra (from bottom to top) were recorded at irradiation times of 15, 30, 60, 90, and 120 min, respectively. No change was observed during the first 14 min.

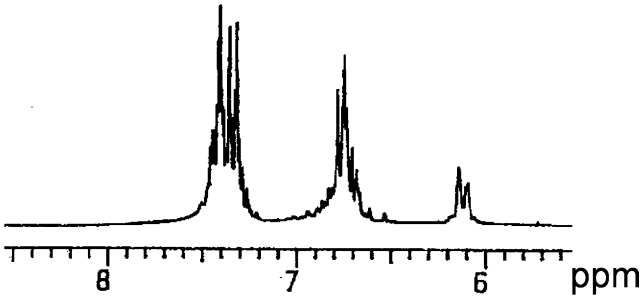


Figure 3. ^{1}H NMR spectrum of the (1*Z*,3*E*) isomer **5**.

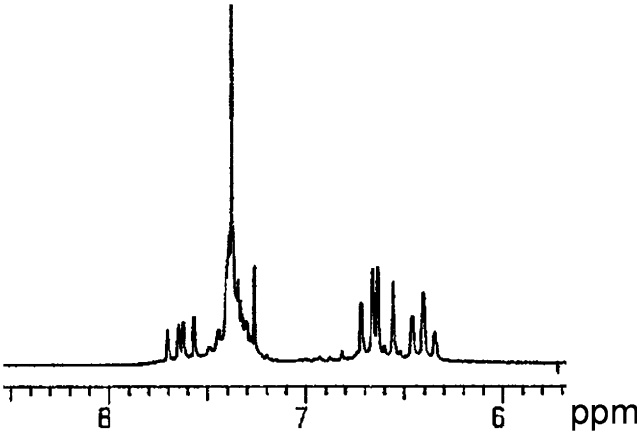


Figure 4. ^{1}H NMR spectrum of the (1*E*,3*Z*) isomer **5**.

tography. The photo-conversion yield (91%) of the (1*E*,3*E*) isomer (**5**) to the (1*Z*,3*E*) isomer at the photostationary state was determined. The result from the direct irradiation of **5** indicated that a dominant cis–trans photoisomerization took place at the carbon–carbon double bond closer to the fluorine substituents.

In Figure 5, the similar UV absorption bands of the three isomers (**1**) are shown. Upon direct irradiation with a Pyrex filter ($\lambda > 300$ nm), the (1*E*,3*E*)-isomer (**1**) in chloroform-*d* (0.015–0.002 M) was also found to photoisomerize at the C=C double bond near the fluorine atom. After purification, the (1*Z*,3*E*)-isomer (**1**) as the only photoproduct was further confirmed by using spectroscopic methods (see Supplementary data). Furthermore, the cis–trans photoisomerization of the (1*E*,3*E*) isomers **2**–**4** was carried out in a manner analogous to **1** and **5**. The data suggested the preferred isomerization at the C=C double bonds closer to fluorine substituents. Also, the photoconversion yield increased as the number of fluorine substituents on the phenyl rings increased (Table 1). At photostationary state, the ratios of (1*Z*,3*E*)/(1*E*,3*E*) of **1**, **2**, **3**, **4**, and **5** were 1:2.6, 1.1:1, 1.6:1, 5.2:1, and 10.1:1, respectively. The results are in accordance with the similar regioselectivity found in photoisomerization of a cyano-substituted

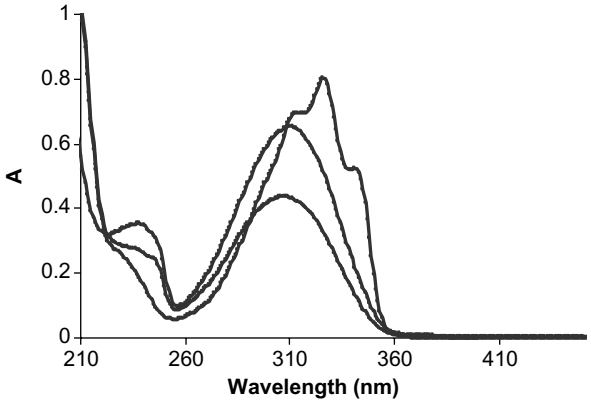


Figure 5. UV absorption maxima of the (1*E*,3*E*), (1*Z*,3*E*), and (1*E*,3*Z*) isomers (**1**) in hexanes are 326, 310, and 307 nm, respectively. The concentrations are varied.

Table 1. The percentages (%) of the *E*/*Z* isomers at photostationary state

Compound	1*E*,3*E*	1*Z*,3*E*	1*E*,3*Z*
1	72	28	0
2	48	52	0
3	39	61	0
4	16	84	0
5	9	91	0

DPB.[7] Moreover, the exclusive formation of the (1*Z*,3*E*) isomers **1**–**5** from photoisomerization of the fluorinated (1*E*,3*E*) isomers was found in other solvents such as hexane and acetonitrile.

The above photo-studies show that photoisomerization of the fluorinated (1*E*,3*E*) isomers **1**–**5** is a regiospecific reaction, and the *E*/*Z* photoisomerization conversion rate is strongly dependent on the number of fluorine substituents on the phenyl rings. As indicated by our computational calculation (DFT-B3LYP/6-31G**), the ground-state energy difference between two *E*,*Z* isomers of the fluorinated DPBs **1**–**5** is less than 1 kcal/mol. Because of the small difference, the observed regioselectivity must be influenced by the photochemical properties of **1**–**5** in the excited singlet state, which are clearly sensitive to the electron-withdrawing fluorine substituents. In 1970, the geometrical relaxation in the excited state of a 1,3-diene caused by a highly polar twisted allylmethylene species (zwitterion) was postulated by Dauben to elucidate the stereoselective cyclization of ethylidenecyclooctene.[10] Since then, the postulated zwitterionic excited states as intermediates have been used to account for the regioselectivity of photoisomerization of some unsymmetrical short polyenes.[11–14] Meanwhile, other explanations have been proposed.[15–17] Due to the polar nature of fluorine substituents, we examined all the possible zwitterionic intermediates. Although the excited zwitterion is short-lived, it could play a crucial role in determining the regioselectivity of photoisomerization.[18,19] Of the four possible zwitterionic intermediates (Fig. 6), it is clear that structures **6a** and **6c** could lead to selective isomerization at the 1,2-bond. However, due to the nature of the substituents in these intermediates, the participation of zwitterionic structure **6c** is most unlikely. Thus, the most preferred zwitterionic intermediate is **6a**, especially while the number of fluorine substituents increases. The preferentially

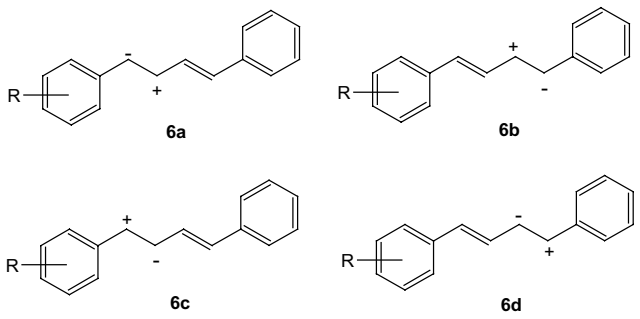


Figure 6. Zwitterionic intermediates.

formed zwitterionic intermediates, which appear to be controlled by fluorine substituents, ultimately determined the specific position of photoisomerization. We believe that the current system involving the different number of polar fluorine substituents further strengthens the fact that the polar character of the excited state has a significant role in directing the position of photoisomerization. In addition, the same regioselectivity of photoisomerization of **1**–**5** found in different solvents states crucial substituent effect as compared to solvent effect.

In summary, we have demonstrated that the selective formation of zwitterionic intermediates, which are sensitive to the substituent effects, controlled the regiospecific photoisomerization of the fluorinated DPBs in the excited singlet state. As mentioned at the beginning of this letter, photoisomerization of all-trans retinal protonated Schiff base (RPSB) in the protein environment (rhodopsin) is regiospecific. In contrast, direct irradiation of all-trans RPSB in solution yields several photoproducts including the main 11-cis isomer. Our results from this study provide useful information for understanding the regioselectivity of photoisomerization of chromophores in solution, which can be potentially applied to other media.[20,21]

Acknowledgments

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Supplementary data

Spectroscopic data (^{1}H NMR, ^{13}C NMR, and UV) of new compounds included in the Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.05.103.

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