The photochemical dimerization of 3-heteroaryl-acrylates

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Abstract

A detailed explanation of the observed photochemical reactivity of 3-heteroaryl-acrylates is furnished on the basis of a comprehensive review of the photochemical dimerizations of this type of compounds. The reactions occurred in the triplet state of the reagents showing good regio- and stereoselectivities. The regioselectivity can be explained assuming that the dimerization reaction is frontier orbitals controlled. The reaction of the triplet state of a reagent with another molecule of the reagent leads to the formation of the most stable biradical. This behavior induces a control in the relative stereochemistry of the two ester functions. The following cyclization occurs in order to obtain the products under kinetic control. This cyclization allows the formation of the most stable isomers.

Keywords: 3-(2-Furyl)acrylates, urocanates, photochemical dimerization

Introduction

The photochemical dimerization of cinnamic acid derivatives in solid state have been the object of an extensive work in the past. On the contrary, the photochemical dimerization of these substrates in solution does not give interesting results. However, the dimerization reaction can be carried out on heterocyclic derivatives to give interesting results.

In this paper we want to account for our work on theoretical aspects of photochemical dimerization of 3-heteroaryl-acrylates in solution in order to give a complete description of this reaction. The heterocyclic ring can play an important role in order to have this type of reaction and in this paper we want to account our results in this field.

The photochemical dimerization of cinnamic acid has been known over 80 years.[1,2] Cinnamic acid (**1**), irradiated in the solid state, gave the corresponding photodimers depending on the crystal form of the starting material: the metastable β-form is reported to yield β-truxinic acid (**2**), while the stable α-form gave α-truxillic acid (**3**) (Scheme 1).[3-7]
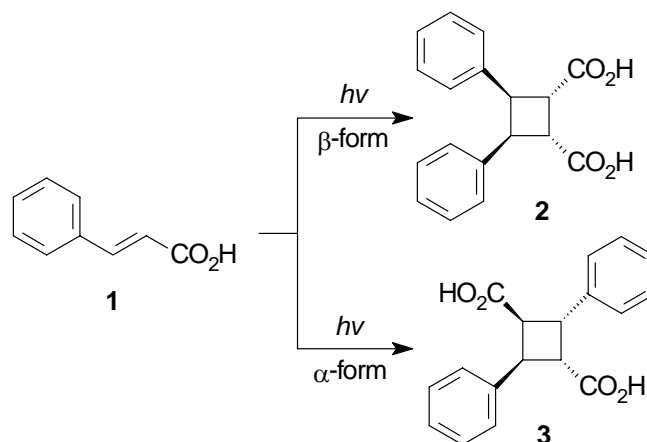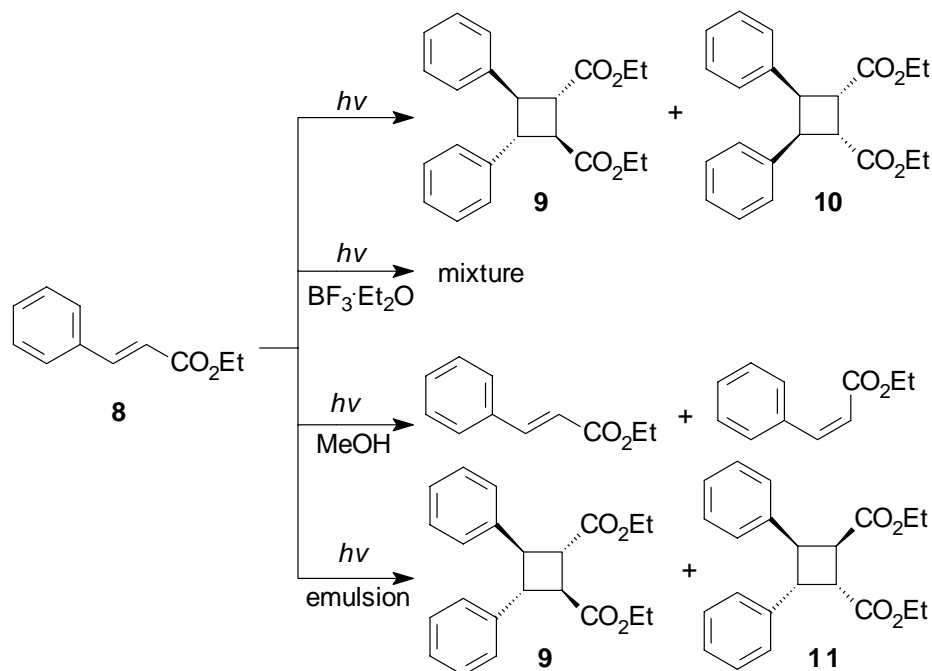
Scheme 1

This type of reaction can also be performed on 3-(2-furyl)acrylic acid (**4**) or on 3-(2-thienyl)acrylic acid (**6**) to give the corresponding photodimers (**5**) and (**7**) if the irradiation is performed in the solid state (Scheme 2).[8] It is noteworthy that these reactions need 30 and 20 days of irradiation, respectively, to give the products. Irradiation of **4** and **7** in solution (MeOH) showed only *E-Z* isomerization of the starting materials.[9]
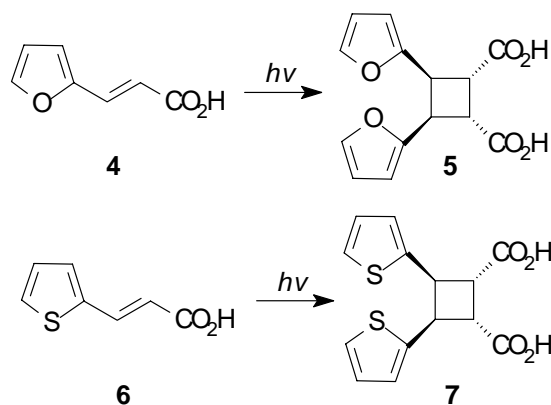
Scheme 2

While the reactivity of cinnamic acid is well defined, the reactivity of the esters is more complex. Irradiation of liquid ethyl cinnamate (**8**) furnished a mixture of two compounds (**9**) and (**10**) in 55 and 25% yields, respectively (Scheme 3).[10,11]
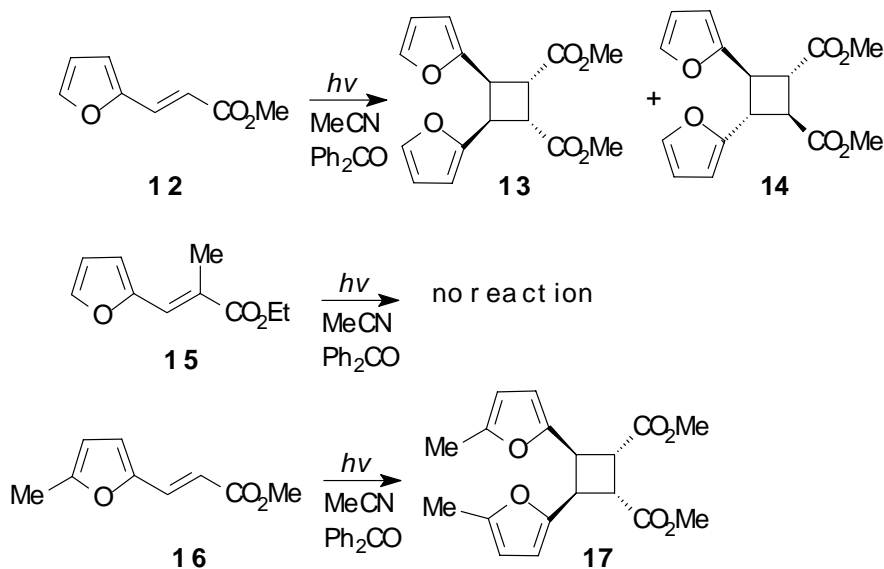
Scheme 3

When the reaction was performed in a mixture of water (82.1%), cyclohexane (3.2%), butanol (9.8%), and sodium dodecyl sulfate (4.9%), an 8:2 mixture of *trans*-diesters (**9**) and (**11**) was obtained (Scheme 3).[12] On the other hand, irradiation in methanolic solution did not furnish any cyclodimerization product, giving instead only *E-Z* isomerization,[13] while irradiation in the presence of BF_3 furnished a mixture of seven immers (Scheme 3).[14,15] However, the application of this methodology to methyl 3,4-dimethoxycinnamate failed.[16] 3,4-Dimethoxycinnamic derivatives can be dimerized only in the presence of cyclodextrin.[17] Recently, we found that methoxy-, dimethoxy-, and trimethoxycinnamate esters can be dimerized in acetonitrile both in the presence or in the absence of a triplet sensitizer.[18]

Discussion

Irradiation of methyl 3-(2-furyl)acrylate (**12**) in acetonitrile in the presence of benzophenone as sensitizer furnished a mixture of two compounds (**13** and **14**) in 61 and 27% yields, respectively (Scheme 4).[19,20] The furyl acrylates (**15**) and (**16**), with a methyl group respectively in an α-position to the carboxylic ester and in an α-position on the furan ring, showed different behaviours. While compound (**15**) did not give any photodimer, its isomer (**16**) furnished only the photodimer (**17**), in 22% yield (Scheme 4).[19]

Scheme 4

We did not observe the formation of products of type (**14**). The presence of substituents on the double bond seems to be incompatible with photodimer formation while, unexpectedly, substitution on the furan ring also depresses the reactivity of the double bond.

Direct irradiation of **12** in an immersion apparatus equipped with a Pyrex filter allowed us to obtain a *Z-E* photostationary equilibrium.[21] In different solvents (acetonitrile, methanol, ethyl acetate, ethanol, and benzene) we observed the formation of 25% *Z* isomer in the reaction mixture but no formation of any dimerization product. *Z-E* isomerization is a very fast reaction. The UV spectrum of **12** showed a strong absorption band at λ 299 nm. When the substrate was irradiated with a mercury lamp without filter for a few seconds, shift of the peak at λ 299 nm to λ 302 nm was observed. This bathochromic shift is maintained even after prolonged irradiation. Laser flash photolysis experiments evidences that direct irradiation of **12** in acetonitrile, ethanol, and benzene did not produce any transient state using both 308 and 347 nm excitation. The only photoproduct obtained by UV irradiation of **12** in benzene, ethanol, and acetonitrile was the *Z* isomer; the photoisomerization quantum yield value (0.4 in benzene at λ_{exc} 313 nm) evidences that *trans→perp* rotation is the main decay process of the excited states of **12**. Since there is no evidence of triplet state population under these experimental conditions, it strongly suggests that only the lowest singlet state is involved in the photoisomerization process.

We carried out the dimerization reactions irradiating a 8.2 x 10^{-2} M solution of **12** in the presence of 3.43 x 10^{-3} M benzophenone in a Rayonet chamber reactor equipped with a Pyrex filter with lamps bearing a spectral output at 350 nm.[21] The *Z* isomer rapidly (10 min) reached 0.65 x 10^{-2} M concentration and maintained this concentration during all our experiments. Dimer formation followed a zero order kinetics in agreement with a sensitized reaction. We obtained *k* = 1.38 x 10^{-3} M s^{-1}. The zero order kinetics strictly depends on the benzophenone concentration.

In fact, experiments in benzene at different benzophenone concentrations gave a linear function.[21]

Using laser flash photolysis apparatus in acetonitrile, the triplet of benzophenone (E_T = 69 kcal mol^{-1}) is efficiently quenched by **12**, which reduces its lifetime from ca. 4 µs to < 40 ns. In the meantime, a new transient species appears in the 380 nm region and decays with a lifetime of 140 ns (first-order kinetic). Since the same transient is sensitized by xanthone (E_T = 74 kcal mol^{-1}) and thioxanthone (E_T = 65 kcal mol^{-1}) it is assigned to the lowest triplet state of **12**. Its fast decay is in agreement with an efficient *trans→perp* rotation. In ethanol, irradiation of benzophenone produces a triplet which has a much shorter lifetime (τ_T *ca.* 100 ns) and a ketyl radical ($\tau_{1/2}$ *ca.* 50 µs). Addition of **12** quenches benzophenone triplet to a τ_T < 30 ns with concomitant formation of a lowest excited triplet state of **12** at 380 nm. The decay of the ketyl radical is not influenced by the concentration of **12** even if its absorption is significantly reduced.[21]

In conclusion, it seems that furylacrylate dimerization reaction occurs in the triplet state of the molecule and that this triplet state is obtained *via* energy transfer from benzophenone.

We have to answer to the question regarding the observed regio- and stereoselectivities of the reaction. We have to explain the reason of the formation of only two isomers from eleven possible dimers.

In order to explain the formation of only head-to-head dimers we have examined the possibility of frontier orbital control in the stereochemical behaviour of methyl 3-(2-furyl)acrylate. We have estimated the HOMO and LUMO energy for this compound by using the AM1-UHF semiempirical method and the results are collected in Table 1.

Table 1. HOMO and LUMO for methyl 3-(2-furyl)acrylate

Electronic State	HOMO (eV)	LUMO (eV)	LSOMO (eV)	HSOMO (eV)
S_0	- 9.20	- 0.83		
T_1			- 6.22	-3.91

Clearly, the best interaction occurs between the LSOMO of the excited triplet state and the HOMO of the fundamental singlet state. The LSOMO for the triplet state of **12** and the HUMO for the fundamental singlet state of the same molecule are depicted in Figure 1.

We can see clearly that, in this case, we have the total superposition between the molecules of the reagents. These data can explain the formation of only head-to-head dimers, because, in the case of head-to-tail dimers, the same superposition is not allowed. While the frontier orbitals allow us to explain regiochemical behaviour of the photochemical reaction, the stereochemistry of the reaction can not be explained on the basis of this theory.
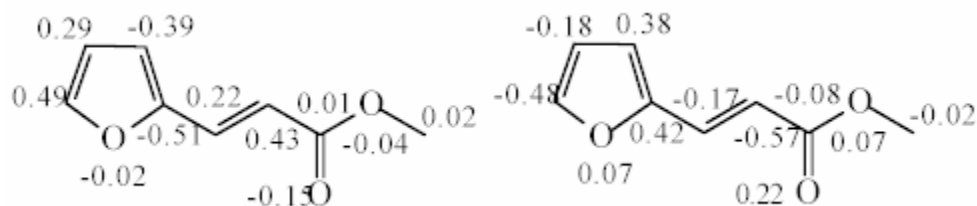
Figure 1

Recently, studying the photodimerization reaction of methyl cinnamate, molecular mechanics calculations showed that the relative stabilities of the dimers are in the order δ(27.12 kcal mol^{-1}) > ξ (28.81 kcal mol^{-1}) > μ (29.48 kcal mol^{-1}) >β (31.98 kcal mol^{-1}). δ-Truxinate ester is the dimer (**9**) while the β-isomer is the dimer (**10**).[22] In our case, we performed molecular mechanics calculations by using MM+ program in HyperChem packet. In this case we observed a completely different trend. In fact, the dimer (**13**) showed a steric energy of 63.86 kcal mol^{-1}, while the dimer (**14**) showed a value of 52.04 kcal mol^{-1}. We observed very different values in the steric energy in comparison with those reported for truxinate esters and these values were higher than those previously reported for the cinnamate dimers.[22] In particular the bending energy was the main cause of this difference. This effect is probably due to the presence of the more polar furan ring in the molecule.

Nevertheless, on the basis of these calculations, the main product of the photochemical dimerization of **12** is less stable than the other product. Then, this approach does not allow us to solve the problem of the stereochemistry of the dimerization reaction.

Table 2. ΔH$_f$ of selected intermediates

Compound	ΔH$_f$ [kcal mol^{-1}]
	-143.98
	-145.31

The reaction leads to the formation of the corresponding triplet biradicals. The coupling of the carbons bearing the electron withdrawing groups determines the stereochemistry of two carbons in the cyclobutane. We verified if this approach is in agreement with the experimental results. We calculated the ΔH$_f$ of the biradical intermediates in the case of methyl 3-(2-furyl)acrylate (**12**). Using **12** we obtained two cyclobutanes with both *Z* and *E* relationship

between the ester functions. The product showing *cis* stereochemistry was favored. The results of our calculations are reported in Table 2.

The formation of the biradical with *anti* stereochemistry between the ester function is favored. $\Delta\Delta H_f$ between the isomers is 1.3 kcal mol^{-1}. Probably this value allows the formation of both isomers. The structure of the more stable biradicals is reported in Figure 2.
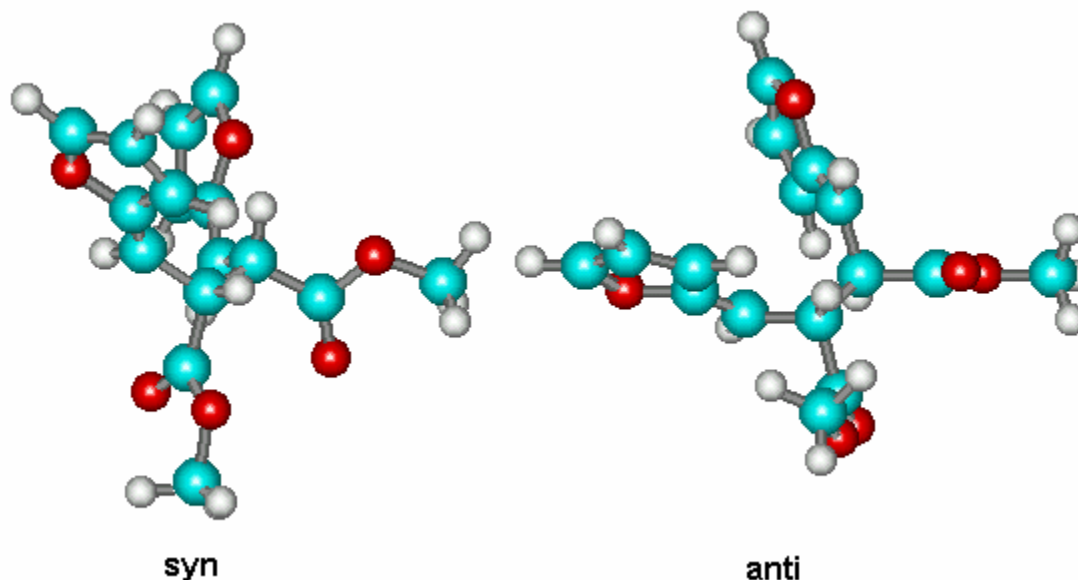

syn   anti

Figure 2

These biradicals can evolve to the formation of the corresponding dimers. We calculated the electronic total energy for all the possible dimers. Calculations were performed by using, also in this case, AM1-UHF semiempirical method. The data are collected in Table 3. We can see that head-to-head dimers are usually more stable than head-to-tail isomers. This could be a further justification of the regiochemical control of the reaction. Furthermore, within head-to-head dimers, the more stable dimers are the obtained ones. Different stability between these two dimers accounts for the different yields observed.

Nevertheless, the ring closure is a kinetic process and, formally, it cannot depend by the thermodynamic stability of the products. To solve this apparent problem, we calculate the energy of the transition state of the ring-closure reactions from the biradical *syn* and *anti*. The biradical *syn* can convert into other three dimers and the biradical *anti* can convert into other three dimers. The obtained results are collected in Table 4. We can see that, when the *syn* biradical is formed, the conversion into the most stable dimer is the kinetically favored reaction. On the same way, when *anti* biradical is formed, the conversion into the more stable dimer is the kinetically favored reaction.

Table 3. Total electronic energy of dimers of methyl 3-(2-furyl)acrylate

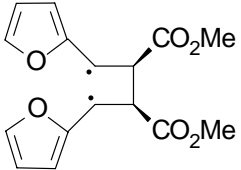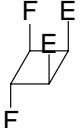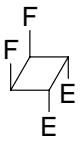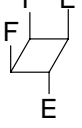| Substrate[a]	-E (kcal mol^{-1})	Substrate[a]	-E (kcal mol^{-1})	Substrate[a]	-E (kcal mol^{-1})
	96448		96482		95265
	95472		96235		96268
	96461		96465		96277
	96272		96472		

(a) F = 2-Furyl, E = CO$_2$Me.
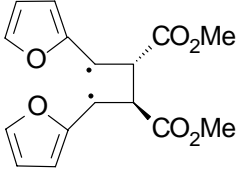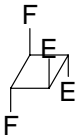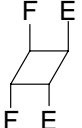
We wanted to verify the effect of a change in the nature of aromatic ring on the reactivity: for this purpose we used the thienyl derivative (**18**). The thienyl derivative (**18**) gave a mixture of two cyclobutane derivatives (**19**) and (**20**) in 1:1 ratio but we obtained these compounds with an overall yield of 25% (Scheme 5).[19] In this case, the best interaction can be obtained between LUMO of the S$_0$ and the HSOMO of T$_1$. However, the superposition of the orbitals is not complete and this fact could explain the low reactivity observed.[23]
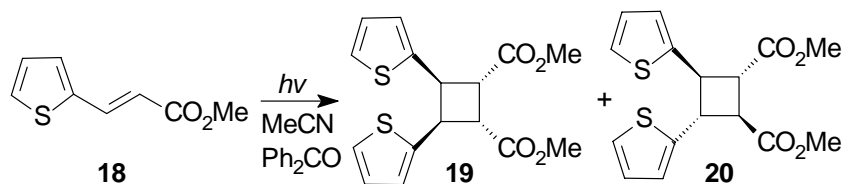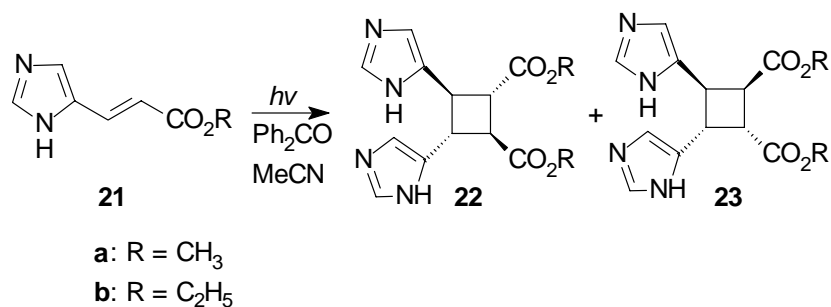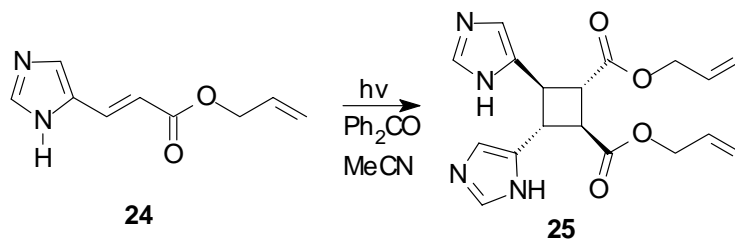

Scheme 5

The irradiation of methyl and ethyl urocanates (**21a-b**) led to the formation of a mixture of two dimers (**22a-b**) and (**23a-b**) (Scheme 6).[24]

Table 4. Transition state energy for the ring closure reaction

Biradical	Dimer	$\Delta H^{\neq}$ [kcal mol^{-1}]
		14.98
		1.28
		9.24
		17.52
		8.04
		10.46

a: R = CH$_3$

b: R = C$_2$H$_5$

Scheme 6

The irradiation of allyl urocanate (**24**) gave an interesting result. In this case the above described regio- and stereoselectivities were enhanced. In fact, we observed the selective formation of only one dimer (**25**) (Scheme 7).[24]

Scheme 7

These experimental data allow us to draw a conclusion. In spite of the previous reported data where only the *Z-E* isomerization of urocanate was described, the presence of benzophenone can sensitize the dimerization of urocanate esters.

Table 5. HOMO and LUMO of imidazolylacrylic derivatives

Compound	Electronic state	HOMO (eV)	LUMO (eV)	LSOMO (eV)	HSOMO (eV)
21a	S_0	- 9.152	- 1.004		
	T_1			- 6.635	- 3.646
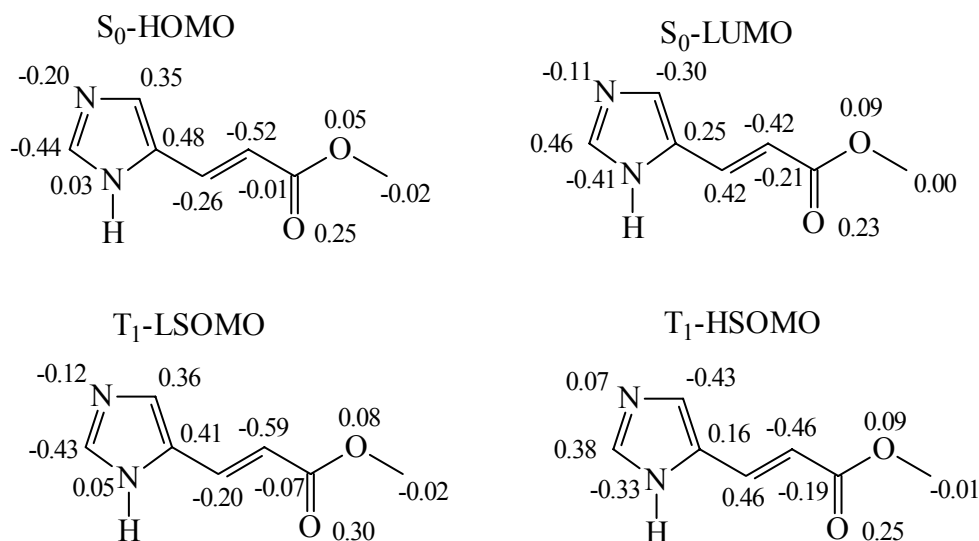
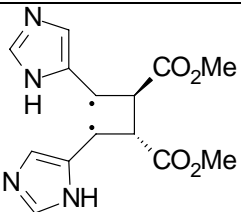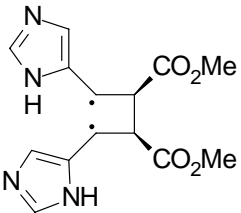**Figure 3.** LSOMO and HSOMO of T_1 and HOMO and LUMO of S_0 of compound (**21a**).

Furthermore, we have to note that the reaction showed a high regio- and stereochemical control. The high stereoselectivity here observed in particular in the case of the dimerization of compound (**24**) was not described before.

The regiochemical behavior can be explained assuming frontier orbital control of the reaction. We estimated the HOMO and the LUMO energies for the compound (**21a**) by using

PM3-RHF-CI semiempirical method and the results are collected in Table 5. In fact, the best interaction occurs between the LSOMO of the excited triplet state and the HOMO of the ground singlet state. The L and HSOMOs for the triplet state and the HOMO and the LUMO for the ground singlet state of the same molecule are depicted in Figure 3.

Therefore, we can see that we have a total superposition between both LSOMO/HOMO and HSOMO/LUMO of the reagents. These data are in agreement with the exclusive formation of head-to-head dimers. The coupling of the triplet state of an urocanate ester with another molecule of the substrate leads to the formation of two possible biradicals. The H_f of these intermediates is reported in Table 6.
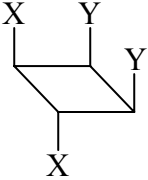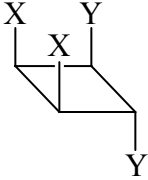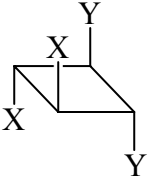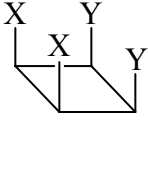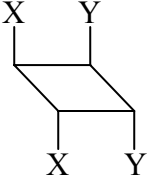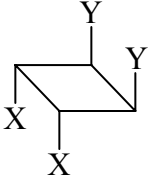
Table 6. ΔH_f of selected intermediates in the urocanate dimerization

Biradical	ΔH_f[kcal mol^{-1}]
	-72.97
	-65.89

The biradical bearing the ester functions in *anti* configuration is more stable than the other one. The energy difference is more relevant in this case than in the case of furylacrylates, explaining the observed high stereoselectivity in the case of urocanate esters: we obtained only dimers with a *trans* relationship between the ester functions.

The stereochemical behavior of the dimerization of methyl urocanate can be explained calculating the heat of formation for all the possible head-to-head dimers. Calculations were performed by using AM1 semiempirical method. The data are collected in Table 7. We can see that the more stable dimers are the obtained ones. Furthermore, different stability between the dimers accounts for different yields observed.

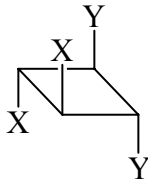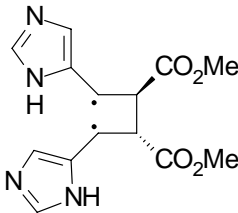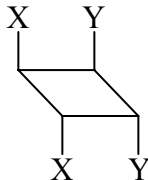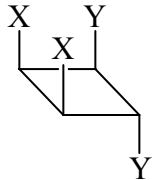**Table 7.** Heat of formation of all the head-to-head dimers of imidazolylacrylates

Dimer	Heat of Formation (kcal mol^{-1})		Dimer	Heat of Formation (kcal mol^{-1})	
	Methyl ester	Allyl ester		Methyl ester	Allyl ester
	-52.42	-8.89		-53.37	-12.85
	-61.74	-16.69		-46.54	-4.21
	-54.64	-5.48		-48.92	-7.71

X = 1*H*-imidazol-4-yl, Y = CO$_2$R

In the case of the allyl ester, the compound which showed the highest stereoselectivity, the data collected in Table 7 are in agreement with the formation of the compound (**25**): in fact, it is the more stable dimer. In this case, the dimer corresponding to the compound (**23a**) was not obtained, and the data reported in Table 7 are in agreement with this result: in fact, this dimer showed ΔH_f = -5.48 kcal mol^{-1} and this value is high if compared with the ΔH_f of the compound (**25**) (-16.69 kcal mol^{-1}).

Furthermore, we did not observe the formation of a dimer with ΔH_f = -12.85 kcal mol^{-1}. In this case, the photochemical behavior of the substrate seems to exclude the formation of dimers with a *cis* relationship between two imidazolyl rings. This behavior can be explained considering the energies of the transition states of the ring-closure reaction of the *anti* biradical. The results are collected in Table 8. The transition state energy for the formation of the dimer with ΔH_f = -12.85 kcal mol^{-1} is too high to allow this reaction.

Table 8. Transition state energy for the ring closure reaction

Biradical	Dimer	$\Delta H^{\neq}$ [kcal mol^{-1}]
		1.24
		2.21
		60.37

The photochemical dimerization of alkenes bearing both pentaatomic aromatic heterocyclic rings and electron withdrawing groups can be understood assuming frontier orbital control of the reaction. This control determines the regiochemical behavior of the dimerization (head-to-head versus head-to-tail products). The reaction occurs through the first excited triplet state. The evolution of the biradicals obtained through the coupling of the carbons bearing the electron withdrawing groups can be understood considering the stability of the cyclobutane rings. In fact, all the reactions tested showed that only the more stable cyclobutanes were obtained. The formation of the more stable isomers can be understood on the basis of the different stability of the biradical intermediates and the transition state energy of the ring-closure reaction.

In conclusion we have shown that the photochemical dimerization in solution of the heterocyclic substituted alkenes bearing electron withdrawing groups can be predicted on the basis of this photophysical and chemical properties.

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