ELSEVIER

Journal of Photochemistry and Photobiology A: Chemistry 112 (1998) 145–148

Journal of Photochemistry and Photobiology A:Chemistry

Photochemical dimerization of esters of urocanic acid

Maurizio D'Auria *, Rocco Racioppi

Dipartimento di Chimica, Università della Basilicata, Via N. Sauro 85, 85100 Potenza, Italy

Accepted 11 October 1997

Abstract

The irradiation of urocanate esters in the presence of benzophenone in acetonitrile with a mercury lamp led to the formation of dimers. Methyl and ethyl urocanate gave a 2:1 mixture of dimethyl or diethyl *c*-3,*t*-4-di-(1*H*-imidazol-4-yl)cyclobutane-r-1,*t*-2-dicarboxylate and dimethyl or diethyl *t*-3,*c*-4-di-(1*H*-imidazol-4-yl)cyclobutane-r-1,*t*-2-dicarboxylate. The allyl urocanate gave in high yields only of diallyl *c*-3,*t*-4-di-(1*H*-imidazol-4-yl)cyclobutane-r-1,*t*-2-dicarboxylate. The regiochemistry of the reaction can be explained considering the frontier orbital interactions. The stereochemistry of the reaction can be justified on the basis of the ΔH_f of the products. In all the cases, the most stable dimers were obtained.

Keywords: Photochemical dimerization; Urocanate esters; Benzophenone

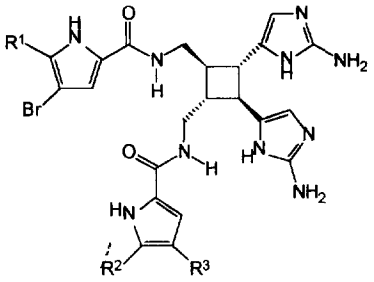
1. Introduction

Urocanic acid is a degradation product of l -histidine and shows some interesting biological properties as light screen [1]. The esters of urocanic acid have been used as UV screen and several applications have been reported in this field [2–8]. Furthermore, the recent photochemical inactivation of infectious DNA by urocanic acid and its esters has been likewise described [9].

Besides its biological properties, the photochemistry of urocanic acid and its derivatives is usually restricted to the study of the *cis–trans* isomerization [10].

A few years ago, we reported that the photochemical irradiation of 3-substituted aryl and heteroaryl 2-propenoic acid derivatives can undergo a photochemical dimerization if irradiated in acetonitrile in the presence of benzophenone [11–14]. Furthermore, this reaction can be used also in the photochemical dimerization of the arylacrylonitrile derivatives [15].

In this paper, we report our results on the photochemical dimerization of esters of urocanic acid. This study can give interesting information in a possible deactivation mechanism of these compounds in sunscreen preparations in the presence of UV-A filters (benzophenone derivatives). Furthermore, this photochemical procedure could represent a way of access to the synthesis of the cyclobutane derivatives **1–3**, isolated from Caribbean sponges *Agelas sceptrum* and *A. conifera*, and characterised by antimicrobial and antibacterial activities [16–18].



1: $R^1 = R^2 = H$, $R^3 = Br$
2: $R^1 = R^2 = R^3 = H$
3: $R^1 = R^2 = R^3 = Br$

2. Materials and methods

2.1. Methyl urocanate

Urocanic acid (3 g, 21.7 mmoles) was dissolved in dry methanol (60 ml) and treated with $BF_3 \cdot Et_2O$ (8.25 ml, 65.1 mmoles). The mixture was refluxed under Ar for 24 h. The reaction mixture was treated with aqueous Na_2CO_3 and extracted four times with CH_2Cl_2. The collected organic phases were dried (Na_2SO_4) and the solvent was removed in vacuo to give 2.9 g of pure methyl urocanate. ^1H NMR [$(CD_3)_2CO$] δ: 8.18 (s, 1 H), 8.04 (d, 1 H, $J = 15$ Hz), 7.96 (s, 1 H), 6.90 (d, 1 H, $J = 15$ Hz), and 4.18 ppm (s, 3 H).

2.2. Ethyl urocanate

Urocanic acid (3 g, 21.7 mmoles) was dissolved in dry ethanol (60 ml) and treated with $BF_3 \cdot Et_2O$ (8.25 ml, 65.1

* Corresponding author.

1010-6030/98/$19.00
PII S1010-6030(97)00292-X

mmoles). The mixture was refluxed under Ar for 24 h. The reaction mixture was treated with aqueous Na_2CO_3 and extracted four times with CH_2Cl_2. The collected organic phases were dried (Na_2SO_3) and the solvent was removed in vacuo to give 2.9 g of pure methyl urocanate. ^{1}H NMR [$(CD_3)_2CO$] δ: 8.20 (s, 1 H), 8.05 (d, 1 H, J=15 Hz), 8.00 (s, 1 H), 6.88 (d, 1 H, J=15 Hz), 4.12 (q, 2 H, J=7 Hz), and 1.17 ppm (t, 3 H, J=7 Hz).

2.3. Allyl urocanate

Urocanic acid (3 g, 21.7 mmoles) was dissolved in allylic alcohol (60 ml) and treated with $BF_3 \cdot Et_2O$ (8.25 ml, 65.1 mmoles). The mixture was refluxed under Ar for 24 h. The reaction mixture was treated with aqueous Na_2CO_3 and extracted four times with CH_2Cl_2. The collected organic phases were dried (Na_2SO_4) and the solvent was removed in vacuo to give 2.9 g of pure methyl urocanate. ^{1}H NMR ($CDCl_3$) δ: 8.77 (s, 1 H), 7.75 (s, 1 H), 7.63 (d, 1 H, J=15 Hz), 7.31 (s, 1 H), 6.48 (d, 1 H, J=15 Hz), 5.93 (ddd, 1 H, J_1=8 Hz, J_2=5 Hz, J_3=3 Hz), 5.34 (d, 1 H, J=8 Hz), 5.23 (d, 1 H, J=5 Hz), 4.69 (d, 2 H, J=3 Hz).

2.4. Dimerization of methyl urocanate

Methyl urocanate (1.38 g) was dissolved in acetonitrile (90 ml) in the presence of benzophenone (400 ml). The mixture was flushed with nitrogen for 1 h. The mixture was then irradiated with a 125-W high-pressure mercury arc (Helios Italquartz) surrounded by a Pyrex water jacket. After 72 h, the solid mass precipitated in the reaction mixture was filtered and recrystallized by EtOH–water to give 880 mg of dimethyl *c*-3,*t*-4-di-(1*H*-imidazol-4-yl)cyclobutane-r-1,*t*-2-dicarboxylate. ^{1}H NMR (DMSO-d_6) δ: 12.27 (s, 1 H), 8.02 (s, 1 H), 7.32 (s, 1 H), 4.03 (s, 3 H), 3.96 (m, 1 H, J_A=9 Hz, J_B=9 Hz, J=9.7 Hz, J'=0.1 Hz), and 3.32 ppm (m, 1 H, J_A=9Hz, J_B=9 Hz, J=9.7 Hz, J'=0.1 Hz). The acetonitrile derived from the reaction mixture was evaporated to give 430 mg of dimethyl *t*-3,*c*-4-di-(1*H*-imidazol-4-yl)cyclobutane-r-1,*t*-2-dicarboxylate. ^{1}H NMR ($CDCl_3$) δ: 7.80 (m, 1 H), 7.58 (m, 1 H), 7.47 (m, 1 H), 3.78 (m, 1 H, J_A=9 Hz, J_B=9 Hz, J=6.3 Hz, J'=0.2 Hz), 3.70 (m, 1 H, J_A=9 Hz, J_B=9 Hz, J=6.3 Hz, J'=0.2 Hz), and 3.48 ppm (s, 3 H).

2.5. Dimerization of ethyl urocanate

Ethyl urocanate (3 g) was dissolved in acetonitrile (90 ml) in the presence of benzophenone (600 ml). The mixture was flushed with nitrogen for 1 h. The mixture was then irradiated with a 125-W high-pressure mercury arc (Helios Italquartz) surrounded by a Pyrex water jacket. After 72 h, the solvent was evaporated and the crude product was chromatographed on silica gel eluting with $CHCl_3$–MeOH 85/15. This way, 1.1 g of diethyl *c*-3,*t*-4-di-(1*H*-imidazol-4-yl)cyclobutane-r-1,*t*-2-dicarboxylate was obtained. ^{1}H NMR (DMSO-d_6) δ: 7.61 (s, 1 H), 6.94 (s, 1 H), 4.93 (s, 1 H),4.16 (q, 2 H, J=7 Hz), 3.66 (m, 1 H, J_A=9 Hz, J_B=9 Hz, J=9.7 Hz, J'=0.1 Hz), 3.45 (m, 1 H, J_A=9 Hz, J_B=9 Hz, J=9.7 Hz, J'=0.1 Hz) and 1.24 (t, 3 H, J=7 Hz). The second product from the column chromatography was diethyl *t*-3,*c*-4-di-(1*H*-imidazol-4-yl)cyclobutane-r-1,*t*-2-dicarboxylate. ^{1}H NMR (Py-d_5) δ: 7.93 (s, 1 H), 7.60 (s, 1 H), 7.08 (s, 1 H), 4.76 (m, 1 H, J_A=9 Hz, J_B=9 Hz, J=6.3 Hz, J'=0.2 Hz), 4.45 (m, 1 H, J_A=9 Hz, J_B=9 Hz, J=6.3 Hz, J'=0.2 Hz), 4.16 (q, 2 H, J=7 Hz), and 1.10 ppm (t, 3 H, J=7 Hz).

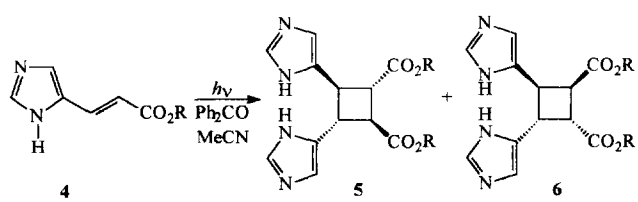
2.6. Dimerization of allyl urocanate

Allyl urocanate (1.5 g) was dissolved in acetonitrile (90 ml) in the presence of benzophenone (400 ml). The mixture was flushed with nitrogen for 1 h. The mixture was then irradiated with a 125-W high-pressure mercury arc (Helios Italquartz) surrounded by a Pyrex water jacket. After 72 h, the solvent was evaporated and the crude product was chromatographed on silica gel. The elution with chloroform – methanol 85:15 gave 1.080 g of diallyl *c*-3,*t*-4-di-(1*H*-imidazol-4-yl)cyclobutane-r-1,*t*-2-dicarboxylate. ^{1}H NMR (DMSO-d_6) δ: 8.64 (s, 1 H), 7.98 (s, 1 H), 6.92 (ddd, 1 H, J_1=8 Hz, J_2=5 Hz, J_3=3 Hz), 6.28 (d, 1 H, J=8 Hz), 6.20 (d, 1 H, J=5 Hz), 6.00 (s, 1 H), 5.65 (d, 2 H, J=3 Hz) 4.73 (m, 1 H, J_A=9 Hz, J_B=9 Hz, J=9.7 Hz, J'=0.1 Hz), and 4.57 ppm (m, 1 H, J_A=9 Hz, J_B=9 Hz, J=9.7 Hz, J'=0.1 Hz).

3. Results and discussion

The esters used in this work were prepared according to a previously reported procedure by using $BF_3 \cdot Et_2O$ as catalyst [19]. The irradiation was carried out in an immersion apparatus by using a 125-W high pressure mercury arc in the presence of a Pyrex filter. As solvent we used acetonitrile according to our previous reports in this field.

The irradiation of methyl and ethyl urocanate **4a–b** led to the formation of a mixture of two dimers (**5a–b**) and (**6a–b**) (Scheme 1, Table 1). The identification of the dimers was performed on the basis of the ^{1}H NMR spectra. The analyses of the ^{1}H NMR spectra of the compounds **5** and **6** is reported in Table 2 on the basis of literature data [20]. In particular, we obtained from the spectra the *N*, *L*, *K*, and *M* parameters.



4 5 6

a: R = CH_3
b: R = C_2H_5

Scheme 1.

Table 1
The photochemical dimerization of imidazol-4-yl acrylates

Substrate	Product	Yield (%) [a]
4a	**5a**	64
	6a	31
4b	**5b**	37
	6b	15
7	**8**	72

[a] All the yields refer to isolated chromatographically pure compounds.

Table 2
Analysis of the AA'BB' part of the ^{1}H NMR spectra of dimeric compounds

Compound	N	L	K	M	J	J'	J_A	J_B
5a	9.8	9.6	18	0	9	9	9.7	0.1
6a	6.5	6.1	18	0	9	9	6.3	0.2
5b	9.8	9.6	18	0	9	9	9.7	0.1
6b	6.5	6.1	18	0	9	9	6.3	0.2
8	9.8	9.6	18	0	9	9	9.7	0.1

These values were used to calculate the coupling constant J (J_{AB} in a AA'BB' system), J' ($J_{AB'}$), J_A ($J_{AA'}$), and J_B ($J_{BB'}$), on the basis of the following equations:

$$K=(J_A+J_B)$$

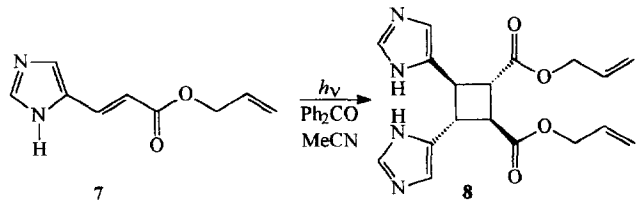
$$M=(J_A-J_B)$$

$$N=(J+J')$$

$$L=(J-J')$$

The obtained values for J were in agreement with a *trans* relationship between the A and B part of the system, while the values of J_A and J_B were in agreement with a *trans* relationship between A and A' and B and B', respectively, when the value is 9.7 Hz and in agreement with a *cis* relationship when the value is 6.3 Hz.

The irradiation of allyl urocanate gave an interesting result. In this case, the above described regio- and stereoselectivity



7 8

Scheme 2.

Table 3
HOMO and LUMO of imidazolyl acrylic derivatives

Compound	Electronic state	HOMO (eV)	LUMO (eV)	LSOMO (eV)	HSOMO (eV)
4a	S_0	−9.152	−1.004		
	T_1			−6.635	−3.646

resulted to enhancement. In fact, we observed the selective formation of only one dimer (**8**) (Scheme 2, Table 1). On the basis of the analysis of the ^{1}H NMR spectrum (Table 2), we could assign the *trans*-2, *cis*-3, *trans*-4 structure.

These experimental data allow us to draw a conclusion. In spite of the previous reported data where only the *cis–trans* isomerization of the substrates was described, the presence of benzophenone (and, obviously, of benzophenone derivatives) usually present in UV-A filter in sunscreen preparations, can sensitize the dimerization of urocanate esters.

Furthermore, we have to note that the reaction showed a high regio- and stereochemical control. It is known that high regio- and stereochemical control in the photochemical dimerization of cinnamic acid can be obtained irradiating in the solid state [21–26]. The high stereoselectivity here, observed in particular in the case of the dimerization of compound **7**, was not described before.

The regiochemical behaviour can be explained assuming frontier orbital control of the reaction. We estimated the HOMO and the LUMO energies for the compound **4a** by using PM3-RHF-CI semi-empirical method and the results are collected in Table 3 [27]. In fact, the best interaction occurs between the LSOMO of the excited triplet state and

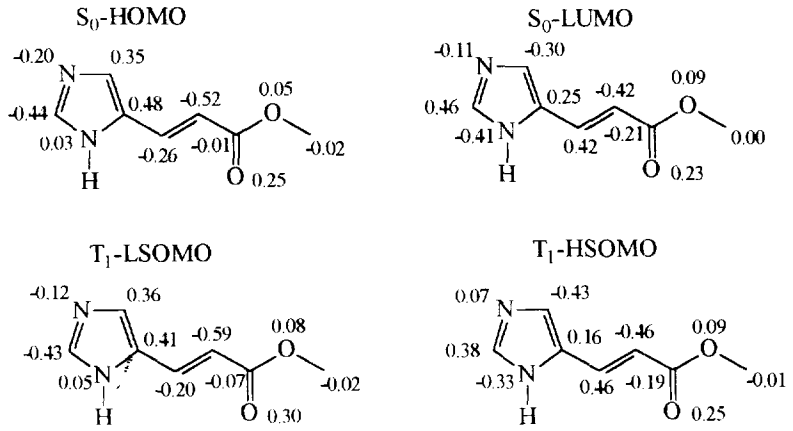
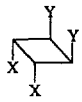


Fig. 1. LSOMO and HSOMO of T_1 and HOMO and LUMO of S_0 of compound **4a**.

Table 4
The heat of formation of all the head-to-head dimers of imidazolyl acrylates

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

X = 1*H*-Imidazol-4-yl, Y = CO_2R.

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 Fig. 1.

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 stereochemical behaviour 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 semi-empirical method [28,29]. The data are collected in Table 4. We can see that the obtained dimers are the more stable ones. Furthermore, the difference in stability between the dimers accounts for the different yields observed.

In allyl ester, the compound which showed the highest stereoselectivity and the data collected in Table 4 are in agreement with the formation of the compound **8**; in fact, it is the more stable dimer. In this case, the dimer corresponding to the compound **6a** was not obtained, and the data reported in Table 4 are in agreement with this result; in fact, this dimer showed that $\Delta H_f = -5.48$ kcal mol^{-1} and this value is high if compared with the ΔH_f of the compound **8** (−16.69 kcal mol^{-1}).

Furthermore, we did not observe the formation of a dimer with $\Delta H_f = -12.85$ kcal mol^{-1}. In this case, the photochemical behaviour of the substrate seems exclude the formation of dimers with a *cis* relationship between two imidazolyl rings. On the basis of our results we can not explain this selectivity.

4. Conclusion

In conclusion, we have seen that urocanate esters can give dimerization reaction in the presence of benzophenone. This result could preclude the use of these compounds in sunscreen in the presence of benzophenone derivatives. Furthermore, the dimerization shows an interesting stereoselectivity that can be explained considering the frontier orbital interaction and the heat of formation of the products. Finally, the stereoselectivity of the reaction of the allyl urocanate offers an interesting substrate for the synthesis of the naturally occurring cyclobutane derivatives **1–3**.

References

[1] M. Luckner, Secondary Metabolism in Microorganisms, Plants, and Animals, Springer-Verlag, Berlin, 1990, p. 455.
[2] I.M. Hais, A. Zenisek, Am. Perfum. Aromat. (1959) 26.
[3] J.H. Anglin, Cosmet. Toiletries 91 (1976) 47.
[4] A. Zenisek, I.M. Hais, E. Marklova, Perfum. Cosmet. Aromat. 24 (1978) 47.
[5] H. Nagamatsu, A. Maekawa, M. Kinami, M. Doi, Jpn. Kokai Tokkyo Koho 07 196 457, 1995.
[6] H. Nagamatsu, A. Maekawa, M. Kinami, M. Doi, Chem. Abstr. 123 (1995) 296239d.
[7] K. Esumi, Y. Hiraki, S. Yoshikawa, Jpn. Kokai Tokkyo Koho 06 09 359 (1994).
[8] K. Esumi, Y. Hiraki, S. Yoshikawa, Chem. Abstr. 120 (1994) 226565w.
[9] T. Mohammad, I. Tessman, H. Morrison, M.A. Kennedy, S.W. Simmonds, Photochem. Photobiol. 59 (1994) 189.
[10] F.D. Lewis, B.A. Yoon, Res. Chim. Intermed. 21 (1995) 749.
[11] M. D'Auria, G. Piancatelli, A. Vantaggi, J. Chem. Soc., Perkin Trans. I, (1990) 2999.
[12] M. D'Auria, A. Vantaggi, Tetrahedron 48 (1992) 2523.
[13] M. D'Auria, A. D'Annibale, T. Ferri, Tetrahedron 48 (1992) 9323.
[14] M. D'Auria, Heterocycles 43 (1996) 959.
[15] M. D'Auria, R. Racioppi, Tetrahedron, in press.
[16] R.P. Walker, D.J. Faulkner, D. van Engen, J. Clardy, J. Am. Chem. Soc. 103 (1981) 6773.
[17] P.A. Keifer, R.E. Schwartz, M.E.J. Koker, R.G. Hughes, D. Rittschof, K.L. Rinehart, J. Org. Chem. 56 (1991) 2965.
[18] K.L. Rinehart, Pure Appl. Chem. 61 (1989) 525.
[19] R. Quinn, J. Mercer-Smith, J.N. Burstyn, J.S. Valentine, J. Am. Chem. Soc. 106 (1984) 4136.
[20] D.M. Grant, R.C. Hirst, H.S. Gutowsky, J. Chem. Phys. 38 (1965) 470.
[21] M.D. Cohen, G.M.J. Schmidt, F.I. Sonntag, J. Chem. Soc., (1964) 2000.
[22] G.M.J. Schmidt, J. Chem. Soc., (1964) 2014.
[23] J. Bregman, K. Osaki, G.M.J. Schmidt, F.I. Sonntag, J. Chem. Soc., (1964) 2021.
[24] G.M.J. Schmidt, Pure Appl. Chem. 27 (1971) 647.
[25] F. Nakanishi, H. Nakanishi, M. Tsuchiya, M. Hasegawa, Bull. Chem. Soc. Jpn. 49 (1976) 3096.
[26] M. Lahav, G.M.J. Schmidt, J. Chem. Soc. B, (1967) 239.
[27] J.P.P. Stewart, J. Comp. Chem. 10 (1989) 221.
[28] M.J.S. Dewar, E.G. Zoebisch, E.F. Healy, J.P.P. Stewart, J. Am. Chem. Soc. 107 (1985) 3902.
[29] M.J.S. Dewar, Y.C. Yuon, Inorg. Chem. 29 (1990) 3881.