Enantioselective photocyclization of *p*-toluidides of α,β-unsaturated carboxylic acids in solution. A mechanistic and preparative study

Pilar Formentín,[a] María J. Sabater,[a] Michelle N. Chrétien,[b] Hermenegildo García *[a] and Juan C. Scaiano *[b]

[a] *Instituto de Tecnología Química CSIC-UPV, Universidad Politécnica de Valencia, Apartado 22012, 46071-Valencia, Spain*
[b] *Department of Chemistry, Centre for Catalysis Research and Innovation, University of Ottawa, Ottawa, K1N 6N5,, Canada*

Received (in Cambridge, UK) 8th June 2001, Accepted 29th October 2001
First published as an Advance Article on the web 27th November 2001

Photolysis of *p*-toluidides of methacrylic (**1a**) and cyclohex-2-enecarboxylic (**1b**) acids in nitrogen-saturated cyclopentane solution yields the corresponding 2-quinolones with over 90% chemoselectivity at almost complete conversion. In the presence of substoichiometric amounts (0.1 equivalents) of chiral inductor, low to moderate enantiomeric excesses (ee) are observed in the photo-product. Ephedrine gave the highest ee (37% ee for the photocyclization of **1a**) in a series of 11 chiral inductors including alcohols, amines, aminoalcohols, α-amino and α-hydroxy acids. In the case of the irradiation of **1b** in the presence of chiral inductors, both diastereo- and enantioselectivity were observed. A weakly absorbing transient species (λ_{max} 400 nm) was detected following 308 nm laser excitation and was assigned to the zwitterionic enolate intermediate resulting immediately after the concerted electrocyclic ring closure. The lifetime of this intermediate is unaffected by oxygen but is quenched by trifluoroacetic acid ($k_q = 3.76 \times 10^7$ M^{-1} s^{-1}) and ephedrine ($k_q = 1.19 \times 10^7$ M^{-1} s^{-1}).

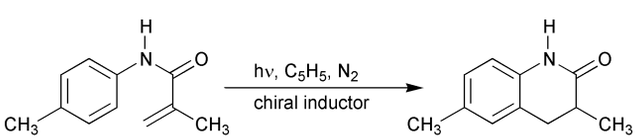
Introduction

Asymmetric photochemistry is attracting much current interest as evidenced by several reviews which have appeared related to this topic.[1–3] In principle, the main advantage of photo-induced enantioselectivity over thermal ground-state reactions is the lower temperature at which the photochemical reactions can be conducted. The photocyclization of acrylanilides to 3,4-dihydroquinolin-2(1*H*)-ones has long been studied[4–6] and has found some application in the synthesis of alkaloids.[7–9] In the present work we report our study on the enantioselective photocyclization of *p*-toluidides of α,β-unsaturated carboxylic acids **1a**,**b** to the corresponding dihydroquinolinones **2a**,**b**. This reaction has been previously studied in solution at 5–10 °C in the presence of chiral inductors derived from tartaric acid and reported to proceed in low enantiomeric excess (13% ee).[10,11] More recently, it has been found that room temperature, solid-state irradiation of 1 : 1 inclusion crystals of acrylanilides in a chiral cyclic acetal of 1,1,4,4-tetraphenylbutanetetrol host results in a 46% yield of the corresponding 2-quinolone with 98% ee.[12,13] The key step of the asymmetric induction in crystals was proposed to be the concerted suprafacial sigmatropic 1,5-H migration from the *ortho* position of the anilide ring to the α-position of the amide C=O group. Remarkably, photochemical *cis–trans* isomerization of the C=C double bond was not observed in the solid-state irradiation of crotonanilide. This photochemical isomerization was the predominant photoprocess for the photolysis of crotonanilides in solution.[14]

In the present work we have combined a product study to assess ee with laser flash photolysis in order to gain insight into the mechanism of the photocyclization. Based on this study, we propose that in solution the key step in chiral induction is asymmetric protonation of the enolate intermediate. This mechanism is different from the concerted sigmatropic H-migration proposed for the solid state irradiation of inclusion crystals.[12,13]

Results and discussion

Anilides **1a**,**b** were obtained by reacting *p*-toluidine with the corresponding acyl chloride and were recrystallized from ethanol before irradiation. Photolysis of *p*-toluidide **1a** in benzene does not lead to any significant conversion after 48 h of irradiation.[15] This could be explained by a filtering effect of the benzene solvent which has a UV absorption spectrum similar to substrate **1a**. In contrast, irradiation of toluidide **1a** in cyclopentane under nitrogen for 2–4 h leads to dihydroquinolinone **2a** with high selectivity at almost complete conversion (Scheme 1). Given the high chemoselectivity of the photochemical reaction under these conditions, we proceeded to perform the irradiation in the presence of a series of chiral inductors. The results are listed in Table 1. The most relevant parameter in this table is the ee for each irradiation. The ee were determined by integrating the area of the HPLC peaks corresponding to each enantiomer using a UV detector monitoring at 256 nm coupled with an on-line polarimeter. The absolute configuration of the predominant stereoisomer was found to be *R*, based on a previous assignment in solution.[11] Analysis of the ee *versus* conversion of substrate **1a** in the presence of (−)-ephedrine indicates that ee is independent of conversion and constant during the irradiation time. Irradiation of an enantiomerically enriched solution of **2a** in cyclopentane showed that no photochemical epimerization of the product occurs under the irradiation conditions. These blank controls

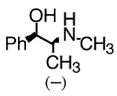
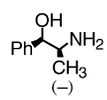
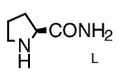
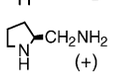


1a **2a**

Scheme 1

 DOI: 10.1039/b105122a

Table 1 Results of the photocyclization of **1a** and **1b** (10^{-3} M) in cyclopentane solution at −40 °C in the presence of a series of chiral inductors (10^{-4} M)

	1a		**1b**		
Chiral inductor	Selectivity (%)	Ee (%)	Selectivity (%)	*cis* : *trans* ratio	Ee[a] (%)
No inductor	96	—	94	1.1	—
 (−)	96	37	93	0.9	26 (2)
 (−)	93	22	74	0.5	14 (3)
 L	96	23	74	0.3	3 (1)
 (+)	94	25	78	0.6	3 (7)

[a] Enantiomeric excesses are given for the *cis* isomer with the value for the *trans* isomer indicated in brackets.

indicate no variation of the ee with extent of conversion or irradiation time, allowing for a straightforward comparison of the ee for each chiral inductor. The highest ee was obtained using ephedrine as the chiral inductor at −40 °C. A decrease in the reaction temperature from 24 to −40 °C has a notable beneficial effect on the resulting ee.

The influence of the chiral inductor concentration at a constant (10^{-3} M) concentration of **1a** was studied for the case of ephedrine at −40 °C. A linear increase of ee with ephedrine concentration was observed at lower concentrations until a limiting ephedrine concentration (~10^{-4} M) is reached, at which point the ee levels off. No further improvement of the ee for **2a** occurs with increased ephedrine concentration. It is noteworthy that the limiting ephedrine concentration is about one order of magnitude lower than the concentration of substrate **1a**.

The fact that the ee for **2a** does not increase continuously with chiral inductor concentration does not support the intermediacy of a substrate-ephedrine complex as previously proposed for the mechanism of asymmetric induction in solution. The fact that the highest ee for **2a** is obtained for substoichiometric amounts of ephedrine suggests that there is a critical step in the mechanism of chiral transmission where the inductor is acting as a catalyst. The previous observation raises the question of the photocyclization mechanism and the actual intermediates involved. This question was addressed by laser flash photolysis.

Upon 308 nm laser excitation of a ~10^{-4} M hexane solution of **1a**, a transient absorption spectrum was recorded (Fig. 1).

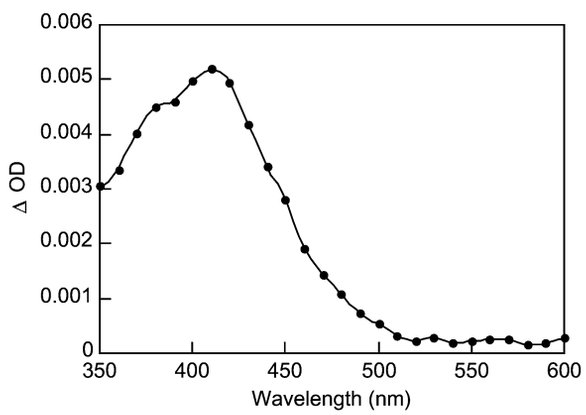
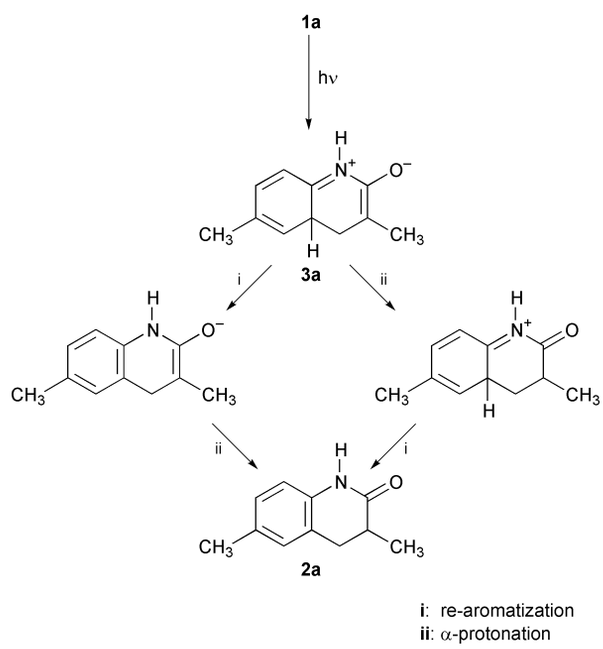


Fig. 1 Transient spectrum recorded 2.88 μs after 308 nm laser excitation of a solution of *p*-toluidide **1a** in hexane (~10^{-4} M) under nitrogen.

The transient was very long lived and did not significantly decay in 2 ms, the longest monitoring time available to our nanosecond system. Assignment of this transient to the intermediate **3a** in Scheme 2 was done based on: (i) the similarity of this



Scheme 2

spectrum to those for related cyclohexadienyl intermediates and a lifetime in the range expected for this type of long-lived intermediate;[16] (ii) the detection of fluorescence from the singlet excited state of compound **1a** that decays on a much shorter time scale (ns) than the transient shown in Fig. 2 and; (iii) the chemical reactivity of this species including the lack of reactivity with oxygen (ruling out a triplet excited state) and quenching by trifluoroacetic acid and ephedrine (see Fig. 2). The zwitterionic intermediate **3a** would be formed by electrocyclic ring closure of the anilide from the α,β-unsaturated carboxylic acid (Scheme 2).

The increased rate of disappearance of the transient in the presence of inductors and acids is particularly relevant in interpreting the results of the asymmetric induction using catalytic amounts of chiral inductor. Since the asymmetric center is created during protonation at the C=O α-position of **3a**, we propose that the role of the chiral inductor is to act as an acid

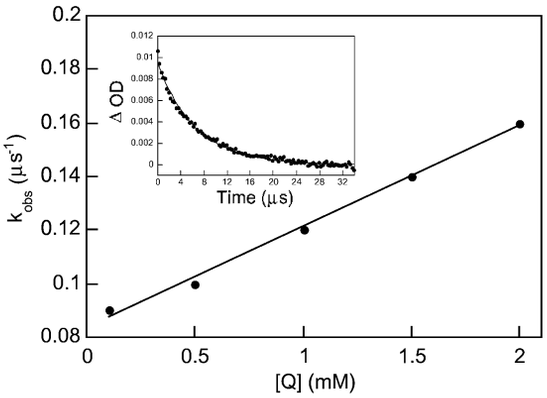
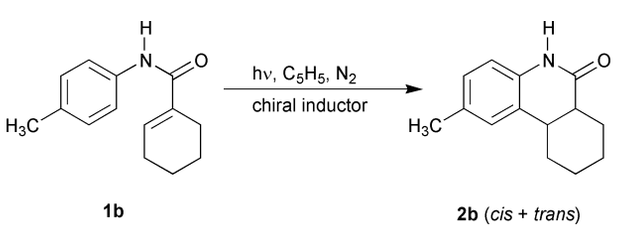


Fig. 2 Plot of k_{obs} *versus* concentration of trifluoroacetic acid (TFAA). Inset: transient decay monitored at 400 nm after 308 nm excitation of a ~10^{-4} M solution of **1a** containing 1.5×10^{-3} M TFAA.

providing the proton in a stereoselective manner. The general range of pK_a values for the species involved in this step is compatible with our proposal.[17] The rate constants for quenching of the observed intermediate by trifluoroacetic acid and (−)-ephidrine were determined to be $k_q = 3.76 \times 10^7$ M^{-1} s^{-1} and $k_q = 1.19 \times 10^7$ M^{-1} s^{-1}, respectively.

This mechanism for asymmetric induction in the photocyclization of anilides in solution is obviously different from that proposed for the enantioselective irradiation of crotonanilide inclusion crystals.[12,13] In the latter case a concerted, stereoselective 1,5-H migration was assumed to be the key step in the photoreaction. The chiral environment provided by the crystal lattice of the host would be responsible for enantioselectivity in the H migration; bimolecular processes are ruled out in the crystalline state. It is obvious that this mechanism for asymmetric induction, based on the immobility of substrate and chiral inductor, cannot operate in solution. Our proposal of asymmetric protonation of a photochemically generated enolate closely resembles the mechanism proposed for the deconjugation of α,β-unsaturated esters[18–21] as well as the Norrish type II dealkylation of α-alkyl substituted indanones.[22,23] In these cases a photochemically generated prochiral enol undergoes enantioselective protonation by a chiral inductor analogous to the mechanism in Scheme 2.[24,25]

We also carried out the irradiation of the *p*-toluidide of cyclohex-2-enecarboxylic acid (**1b**). The cyclic structure of the α,β-unsaturated carboxylic acid will avoid the occurrence of C=C double bond photoisomerization that could disguise the asymmetric induction by concurrent photocyclization of *trans* as well as *cis* isomers in solution. In the case of **1b**, two asymmetric centers are concurrently formed in the photocyclization. The enantioselective photocyclization of anilides related to **1b** has been previously studied in solution[11] as well as in inclusion crystals.[12] As with **1a**, the only product observed was the corresponding dihydroquinolinone **2b** as a mixture of *cis* and *trans* stereoisomers (Scheme 3). The results obtained are also collected in Table 1.



1b **2b** (*cis* + *trans*)

Scheme 3

As can be seen in Table 1, photocyclization of **1b** to the *cis*- and *trans*-quinolones **2b** also occurs with a high chemoselectivity at almost complete substrate conversions. The reaction in the absence of chiral inductor gave a *cis* : *trans* diastereomeric ratio close to 1. It is clearly demonstrated in Table 1 that the nature of the chiral inductor distinctively influences both the diastereomeric ratio and the ee. The *trans* was the preferred diastereomer for irradiations in the presence of chiral inductors and different ee were measured for each *cis* and *trans* isomer. This indicates that the chiral inductor favors a certain configuration of the β-carbon at the electrocyclic ring closure.

In conclusion, photocyclization of anilides of α,β-unsaturated carboxylic acids in solution in the presence of chiral inductors affords the corresponding 3,4-dihydro-2(1*H*)-quinolones with essentially total chemoselectivity and with low to moderate enantiomeric and diastereomeric selectivities. Among the series of chiral inductors, ephedrine in substoichiometric concentrations at low temperature yielded the highest ee (37%) for the irradiation of the *p*-toluidide of methacrylic acid. We propose that the process by which the chiral induction occurs in solution is different from that reported for the irradiation of inclusion crystals in the solid state. A transient was detected for the first time by laser flash photolysis and assigned to the prochiral, zwitterionic, enolate intermediate arising from the electrocyclic ring closure. The fact that this transient reacts with acids suggests that chiral induction occurs by asymmetric protonation at the α-carbon of the enolate rather than through a concerted 1,5-H migration.

Experimental

Synthesis of anilides 1a,b

Thionyl chloride (1.70 g, 14 mmol) was added to a solution of methacrylic or cyclohex-2-enecarboxylic acid (10 mmol) in CCl_4 (20 ml) and the mixture magnetically stirred at room temperature for 2 h. After this time, the solution was concentrated under reduced pressure and a fresh aliquot of CCl_4 was added and removed under vacuum to reduce the residual amount of $SOCl_2$ present. A solution of toluidine (10 mmol) dissolved in CH_2Cl_2 (20 ml) was added to this crude mixture containing the corresponding acyl chloride, and the mixture stirred at room temperature for 2 h. After this time, the solvent was removed under reduced pressure and the resulting solid was recrystallized from EtOH. Toluidides **1a**,**b** were fully characterized by combustion chemical analysis (C, H and N) and by their IR, ^{1}H NMR, ^{13}C NMR, and MS spectroscopic properties. All the data were in agreement with their structure (*vide infra*).

Irradiation procedure

A solution of toluidides **1a**,**b** in cyclopentane (200 ml) was purged with a nitrogen stream for at least 15 min before irradiation. Photolyses were carried out in quartz tubes under magnetic stirring using a 125 W medium pressure mercury lamp. The irradiation vessel was maintained at the required temperature using a cryostat. The course of the reaction was periodically followed by analyzing the photolysis mixture using an isochratic Waters HPLC coupled with a polarimeter and a UV detector monitoring at 256 nm. For the HPLC analyses of the reaction mixtures a chiral column (CHIRALCEL OB) and a 4 : 1 mixture of THF and *i*-PrOH as eluent were used. At the end of the irradiation, the solvent was removed using a rotary evaporator and the residue analyzed by ^{1}H and ^{13}C NMR (Varian Gemini+, 300 MHz) in $CDCl_3$. The residue was also analyzed by GC-MS (HP 5644 A) using a 25 m capillary column of 5% cross-linked phenylmethylsilicone. The corresponding photo-products were spectroscopically characterized. In the case of the irradiation of substrate **1b**, the corresponding 2-quinolone was characterized as a mixture of *cis* and *trans* stereoisomers.

Laser flash photolysis

Samples were excited with 308 nm pulses (6 ns pulse width, ~85 mJ per pulse) from a Lumonics EX-530 excimer laser using a Xe–HCl–Ne mixture. Signals from the monochromator/photomultiplier were captured by a Tektronix 2440 digitizer and transferred to a PowerMacintosh computer programmed in the LabVIEW 4.1 environment from National Instruments. Detailed descriptions of similar laser systems have been provided elsewhere.[26,27] Solutions of toluides **1a** and **1c** in spectroscopic grade hexane (~10^{-4} M) were fully deaerated in Suprasil 7 × 7 mm quartz cells for 20 minutes prior to photolysis. All measurements were recorded using a flow system to avoid the complications of photo-product build-up. The emission spectrum of compound **1a** was measured at room temperature in nitrogen-purged cyclopentane solution with an Edinburgh FS900 spectrofluorimeter using a Xe lamp as the excitation source. The emission decay was shorter than the ns response time of the instrument.

Analytical and spectroscopic data of compounds 1a,b

***N*-(4-Methylphenyl)-2-methylprop-2-enamide (1a).** IR (KBr, cm^{-1}): 3257, 1659, 1623, 1587, 1511, 1393, 1326, 1239, 1111, 932, 814, 507; ^{1}H NMR (δ, $CDCl_3$): 2.06 (t, 3H, J = 0.9 Hz), 2.32 (s, 3H), 5.45 (d, 1H, J = 0.75 Hz), 5.78 (d, 1H, J = 0.84 Hz), 7.10 (m, 2H), 7.44 (m, 2H); ^{13}C NMR (δ, $CDCl_3$): 18.73, 20.82, 119.65, 120.08, 129.42, 133.99, 135.16, 140.85; MS (*m*/*z*): 175 (M^+), 160 (M − 15), 106 (M − 69), 77 (M − 98); chemical analysis: C 74.77%, H 7.92%, N 8.08%; calcd. for $C_{11}H_{13}NO$: C 75.42%, H 7.43%, N 8.00%.

***N*-(4-Methylphenyl)cyclohex-1-enecarbamide (1b).** IR (KBr, cm^{-1}): 3277, 2929, 2857, 1654, 1623, 1593, 1511, 1403, 1316, 1255, 804, 691, 507; ^{1}H NMR (δ, $CDCl_3$): 1.58–1.75 (m, 8H), 2.31 (s, 3H), 6.75 (s, 1H), 7.13 (m, 2H), 7.43 (m, 2H); MS (*m*/*z*): 215 (M^+), 109 (M − 106), 77 (M − 138); chemical analysis: C 78.01%, H 8.40%, N 6.60% N; calcd. for $C_{14}H_{17}NO$: C 78.13%, H 7.90%, N 6.51%.

Acknowledgements

Financial support by the Canadian NSERC through an operating grant (J.C.S.) and to the Spanish DGICYT (H.G., project MAT00–1676–CO2) is gratefully acknowledged. M.J.S. also thanks the Generalidad Valenciana for funding (GVDOC99-0203).

References

1 H. Rau, *Chem. Rev.*, 1983, **83**, 535.
2 Y. Inoue, *Chem. Rev.*, 1992, **92**, 471.
3 S. R. L. Everitt and Y. Inoue, in *Organic Molecular Photochemistry*, eds. V. Ramamurthy and K. S. Schanze, Marcel Dekker, New York, 1999, p. 71.
4 Y. Ogata, K. Takaki and I. Ishino, *J. Org. Chem.*, 1971, **36**, 3975.
5 J. D. Coyle, *Chem. Rev.*, 1978, **78**, 97.
6 A. Gilbert and J. Baggot, *Essentials of Molecular Photochemistry*, Blackwell, Oxford, 1991.
7 J. F. Wolfe and M. A. Ogliaruso, in *The Chemistry of Functional Groups*, ed. S. Patai, John Wiley and Sons, Chichester, 1979, vol. 2, part B, p. 1063.
8 A. G. Schultz, *Acc. Chem. Res.*, 1983, **16**, 210.
9 I. Ninomiya and T. Naito, in *Advances in Heterocyclic Chemistry*, ed. A. Brossi, Academic Press, San Diego, 1983, vol. XXII, p. 189.
10 I. Ninomiya, S. Yamauchi, T. Kiguchi, A. Shinohara and T. Naito, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2285.
11 T. Naito, Y. Tada and I. Ninomiya, *Heterocycles*, 1984, **22**, 237.
12 K. Tanaka, O. Kakinoki and F. Toda, *J. Chem. Soc., Chem. Commun.*, 1992, 1053.
13 H. Hosomi, S. Ohba, K. Tanaka and F. Toda, *J. Am. Chem. Soc.*, 2000, **122**, 1818.
14 M. C. Barbera, H. Garcia, M. A. Miranda and J. Primo, *An. Quim.*, 1995, **91**, 95.
15 Previous studies of the enantioselective photocyclization of acrylanilides were carried out in benzene–ethyl ether, 3 : 1.
16 A. Sanjuan, M. Alvaro, H. Garcia and J. C. Scaiano, *J. Am. Chem. Soc.*, 1998, **120**, 7351.
17 J. March, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, John Wiley and Sons, New York, 1995.
18 O. Piva, R. Mortezaei, F. Henin, J. Muzart and J.-P. Pete, *J. Am. Chem. Soc.*, 1990, **112**, 9263.
19 R. M. Duhaime, D. A. Lombardo, I. A. Skinner and A. C. Weedon, *J. Org. Chem.*, 1985, **50**, 873.
20 R. Mortezaei, O. Piva, F. Henin, J. Muzart and J.-P. Pete, *Tetrahedron Lett.*, 1986, **27**, 2997.
21 F. Henin, J. Muzart, J.-P. Pete and O. Piva, *New J. Chem.*, 1991, **15**, 911.
22 O. Piva, *J. Org. Chem.*, 1995, **60**, 7879.
23 F. Henin, J. Muzart, J.-P. Pete, A. M'oungou-M'assi and H. Rau, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 416.
24 L. Duhamel, P. Duhamel, S. Fouquay, J. J. Eddine, O. Peschard, J. C. Plaquevent, A. Ravard, R. Solliard, J. Y. Valnot and H. Vincens, *Tetrahedron*, 1988, **44**, 5495.
25 C. Fehr and J. Galindo, *J. Am. Chem. Soc.*, 1988, **110**, 6909.
26 J. C. Scaiano, *J. Am. Chem. Soc.*, 1980, **102**, 7747.
27 J. C. Scaiano, M. Tanner and D. Weir, *J. Am. Chem. Soc.*, 1985, **107**, 4396.