Pergamon

Tetrahedron 54 (1998) 6929–6938

TETRAHEDRON

Synthesis of Substituted Benzoquinolines by the Irradiation of 3-Amino-2-alkene Imines

Pedro J. Campos,* Elena Añón, M. Carmen Malo, Cheng-Quan Tan† and Miguel A. Rodríguez

Departamento de Química. Universidad de La Rioja. 26071-Logroño. Spain

Received 27 March 1998; accepted 20 April 1998

Abstract: The irradiation of 3-(naphthylamino)-2-alkene imines allows the preparation of substituted benzoquinolines with good to high yields. The reaction can be extended to include polycyclic azacompounds that contain four rings and is suitable for the preparation of halogenated benzoquinolines that can be functionalized further to give derivatives with pharmacological activity.

Keywords: 'Imines', 'Quinolines'

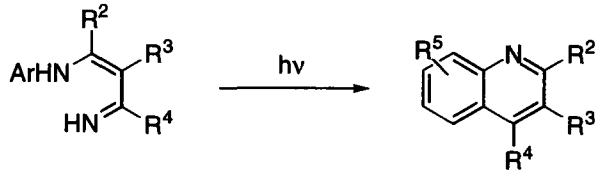
INTRODUCTION

The quinoline ring system occurs in natural products, specially alkaloids,[1] and much attention is still being paid to the synthesis of quinoline derivatives[2] because of their pharmacological properties. In particular, the benzoquinoline skeleton is found in many substances with biological activity or industrial applications. For example, acridine derivatives are effective against infectious microbes, have produced some improvements in Alzheimer's disease, and display good antipsychotic activity; benzo[*f*]quinolines derivatives have marked anti-Parkinson activity and are used in the chemotherapy of the mind.[3]

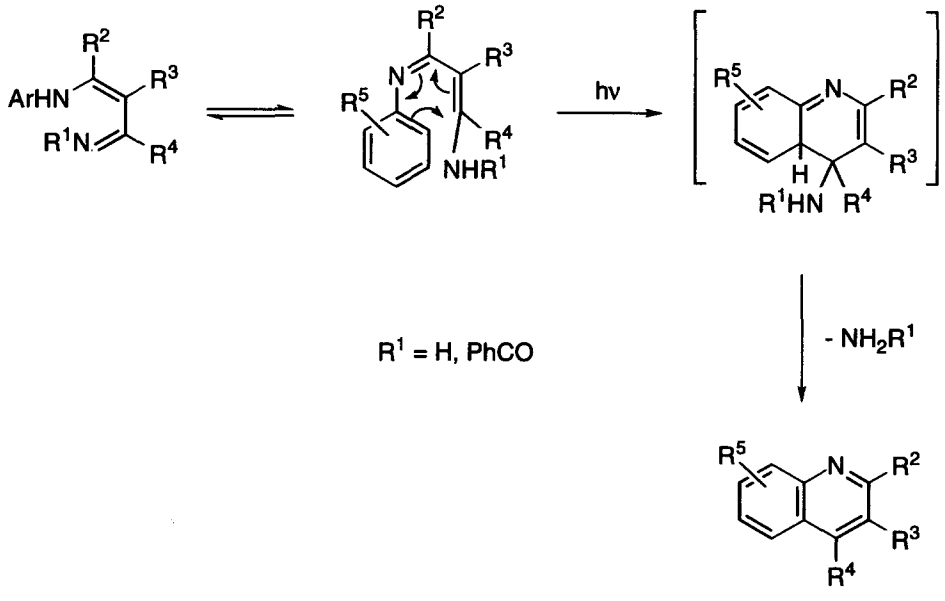
† Present address: University of Dalian. Dalian. China.

0040-4020/98/$19.00
PII: S0040-4020(98)00374-3

We have previously described the irradiation of 3-amino-2-alkene imines to give substituted quinolines[4] and 3-haloquinolines[5] (Scheme 1). Taking into account that the active band in the photochemically induced cyclization is a $\pi \rightarrow \pi^*$ electronic transition and the results are the same regardless of the solvent used (tetrahydrofuran, methanol, benzene) we have proposed that the reaction occurs through a six-electron electrocyclic process as shown in Scheme 2.



Scheme 1

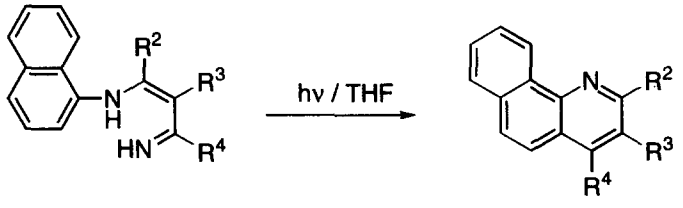


Scheme 2

Given the significance of the benzoquinoline substrates, and in order to explore the generality of the method, we undertook the extension of this methodology to include the preparation of polycyclic systems containing the quinoline ring. In this context, we report here the synthesis of benzoquinolines from irradiation of 3-amino-2-alkene imines.

RESULTS AND DISCUSSION

Looking at the reaction described in Scheme 1, the simplest way to obtain quinolines condensed with a benzo ring should be the inclusion of the benzo unit in the ring that participates in the electrocyclization induced by ultraviolet light. Thus, in order to carry out the reaction in a neutral medium, we first prepared the 2-methyl-3-(1-naphthylamino)-1,3-diphenyl-2-alkene imine **1a**,[6] in which, according to Scheme 1, the naphthyl group should be the active ring in the cyclization. The data obtained from the ultraviolet absorption spectrum (methanol: λ=212, and 350 nm, $\varepsilon\approx$44000, and 11000, respectively) of **1a** are related to those described for the alkene imines previously used,[4] and this prompted us to perform the irradiation of this compound under the same experimental conditions (2×10^{-2} M solution, medium-pressure mercury lamp, quartz). After complete consumption of **1a** (1 mmol, 20 h, monitored by ^{1}H NMR spectroscopy), this reaction yielded the benzo[*h*]quinoline **2a**, as shown by the spectroscopic data (^{1}H and ^{13}C NMR) and mass spectrometry (Scheme 3). Likewise, benzo[*h*]quinoline **2b** was obtained by irradiation of alkene imine **1b** for 20 h.

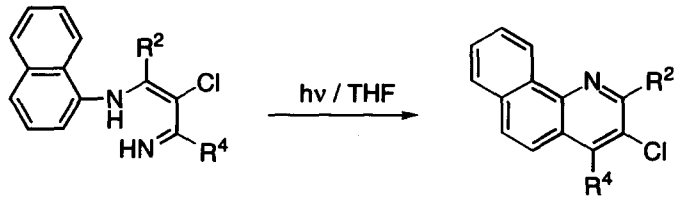


1 **2**

a	R^2 = Ph, R^3 = Me, R^4 = Ph	(84 %)
b	R^2 = Ph, R^3 = Me, R^4 = *p*-MeC_6H_4	(81 %)

Scheme 3

We have also verified the feasibility of this reaction in the synthesis of benzoquinolines carrying a halogen. Thus, the irradiation of 2-chloro-2-alkene imines **1c** and **1d**[7] (methanol: λ=205-215, 250-260, and 360-370 nm, $\varepsilon\approx$55000, 20000, and 7000, respectively) for 4 h in THF gives the corresponding chlorobenzo[*h*]quinolines **3c** and **3d**, respectively, in almost quantitative yields (Scheme 4). Dechlorination was not observed under these experimental conditions.[5] These chloro-derivatives are particularly interesting since they can be functionalized further.[8]

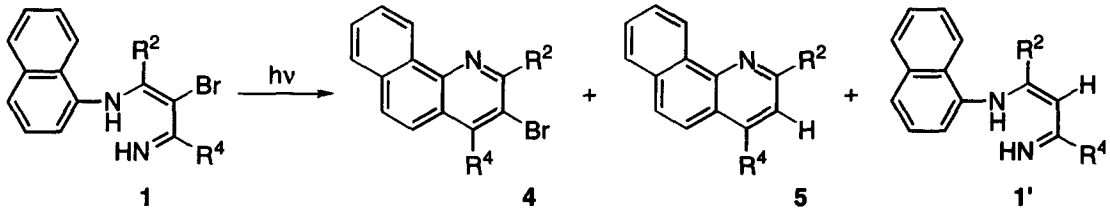


1 3

c	R^2 = Ph, R^4 = Ph	(83 %)
d	R^2 = Ph, R^4 = *p*-MeC_6H_4	(86 %)

Scheme 4

The irradiation of the brominated compound **1e** in tetrahydrofuran led to the formation of bromoquinoline **4e** and debrominated quinoline **5e** together with traces of the alkenimine resulting from the bromine atom photocleavage **1'e** (Scheme 5). Direct irradiation of this debrominated alkenimine **1'e** (prepared according to ref 6) for 20 h led to polymeric material but quinoline **5e** was not observed.[9,10] Therefore, the quinoline **5e** appears to be produced by bromine loss after cyclization. The photodebromination from **4e** would then occur through a mechanism involving an electron transfer from a nucleophile followed by hydrogen transfer from the solvent.[11] The electron transfer process is favored on increasing the solvent polarity.[12] Thus, the debromination process is slowed in benzene (Scheme 5). The increase in the reaction time can be explained by the energy loss due to benzene absorption. The same trend was observed for bromoalkene imine **1f**.

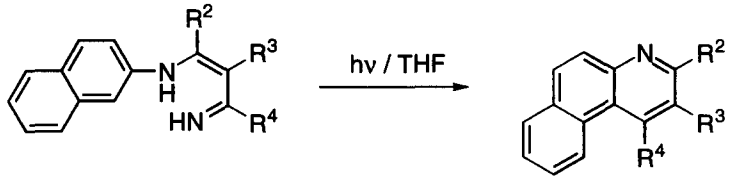


1 4 5 1'

1		Solvent	Time (h)	4 (%)	5 (%)	4/5 ratio
e	R^2 = Ph, R^4 = Ph	THF	4	41	40	1:1
e	R^2 = Ph, R^4 = Ph	Benzene	8	60	21	1:0.4
f	R^2 = Ph, R^4 = *p*-MeC_6H_4	THF	4	45	38	1:0.9
f	R^2 = Ph, R^4 = *p*-MeC_6H_4	Benzene	8	63	19	1:0.4

Scheme 5

In the same way, our methodology allows the preparation of benzo[*f*]quinolines **6g** and **6h** from irradiation of 3-(2-naphthylamino)-2-alkene imine derivatives **1g** and **1h**[6,7] for 4 and 22 h, respectively (Scheme 6). Only the regioisomers represented in Scheme 6 were detectable in the crude mixture (^{1}H NMR, 300 MHz). This regiochemistry is related to other photocyclizations of conjugated arylolefins described in the literature.[13] Compound **6h** was obtained together with a large amount of polymeric material.



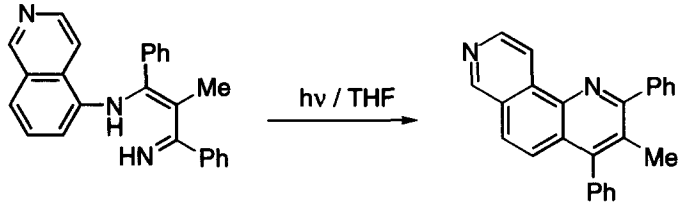
1 **6**

g R^2 = Ph, R^3 = Cl, R^4 = Ph (76 %)

h R^2 = Ph, R^3 = Me, R^4 = *p*-MeC_6H_4 (17 %)

Scheme 6

The reaction is also suitable for the synthesis of polycyclic compounds that contain several heteroatoms, as shown in Scheme 7. Thus, ultraviolet light induces the photocyclization of 3-(5-isoquinolylamino)-2-methyl-1,3-diphenyl-2-alkene imine **1i**[6] to give the corresponding pyrido[3,4-*h*]quinoline **7i**.

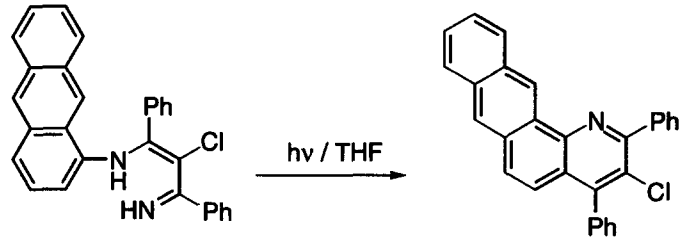


1i **7i** (63%)

Scheme 7

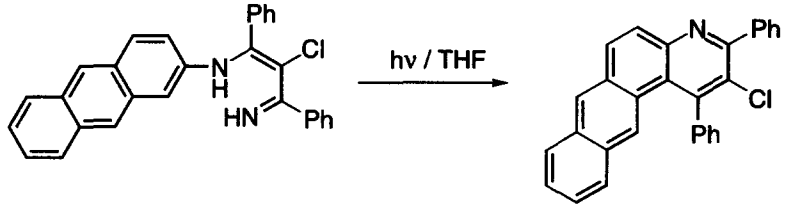
Finally, we wanted to test the validity of the method in the preparation of fused polycyclic azacompounds that contain four rings. We therefore prepared the 3-(1-

anthrylamino)-2-chloro-2-alkene imine **1j**[6,7] (methanol: λ=206, 258, and 388 nm, ε≈38000, 74000, and 8000) and subjected it to ultraviolet light for 4 h in THF. This led to the formation of the naphtho[3,2-*h*]quinoline **8j**,with a good yield (Scheme 8). In the same way, we synthesized the analogue naphtho[3,2-*f*]quinoline **9k**, as the only regioisomer,[13] from irradiation of 3-(1-anthrylamino)-2-chloro-2-alkene imine **1k**[6,7] (Scheme 9). Dechlorination was not observed under these experimental conditions.[5]



1j **8j** (68 %)

Scheme 8



1k **9k** (76 %)

Scheme 9

In conclusion, the irradiation of 3-(naphthylamino)-2-alkene imines allows the regioselective preparation of substituted benzo[*f*]- and benzo[*h*]quinolines giving good to high yields. Due to the mild nature of the reaction conditions and its simplicity and cleanness, we anticipate that this procedure will prove to be widely applicable. In addition, this reaction can be extended to include polycyclic azacompounds that contain more than three rings or several heteroatoms and is suitable for the preparation of halogenated benzoquinolines that can be further functionalized to give derivatives with pharmacological activity. The experimental and theoretical study of the reaction mechanism for the cyclization process are in progress.

EXPERIMENTAL

^1H and ^{13}C spectra were recorded on a Bruker ARX-300 spectrometer in $CDCl_3$ with TMS as internal standard. Electrospray mass spectra were obtained on an HP 5989 B apparatus with an HP 59987 A interface, in positive-ion mode with methanol-water-acetic acid (60:35:5) as the mobile phase. All solvents were purified by standard procedures and freshly destilled prior to use. Reagents were of commercial grades (Aldrich). 3-Amino-2-alkene imines were prepared in accordance with the method described in ref 6, and chloro- and bromoalkene imines according to ref 7.

General procedure for the irradiation of 3-amino-2-alkene imines. A solution of 3-amino-2-alkene imine **1** (1 mmol) in anhydrous THF (50 mL) was irradiated, at room temperature under an Ar atmosphere, using a medium-pressure mercury lamp (125 W) until the complete consumption of the starting material had occurred (quartz: 20-22h for **1a-b** and **1h-i** and 4h for **1c-g** and **1j-k**, monitored by ^1H NMR spectroscopy. Irradiation through Pyrex glass gives the same results but with increased reaction times). The solvent was evaporated under reduced pressure and the residue was extracted with Et_2O (3 x 25 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. The resulting products were separated and/or purified by column chromatography (silica gel, hexane/Et_2O, 3:1) and recrystallized (hexane/Et_2O). The yields described refer to isolated products, relative to starting material **1**. Benzoquinoline **4/5** ratios were determined by ^1H NMR spectra of the crude reaction.

3-Methyl-2,4-diphenylbenzo[*h*]quinoline 2a. mp 178-180 °C; ^1H NMR ($CDCl_3$) δ 2.3 (3H, s), 7.3-7.8 (15H, m), 9.4 (1H, d, J = 8.0Hz); ^{13}C NMR ($CDCl_3$) δ 158.3, 148.1, 144.0, 141.8, 138.1, 133.0, 131.6, 129.6, 129.3, 128.6, 128.6, 128.0, 128.0, 127.9, 127.7, 127.4, 127.1, 126.7, 124.8, 124.2, 123.5, 18.7; ESMS *m/z* 346 (MH^+).

3-Methyl-2-phenyl-4-*p*-tolylbenzo[*h*]quinoline 2b. mp 145-146 °C; ^1H NMR ($CDCl_3$) δ 2.3 (3H, s), 2.5 (3H, s), 7.2-7.8 (14H, m), 9.4 (1H, d, J = 7.5Hz); ^{13}C NMR ($CDCl_3$) δ 158.3, 148.3, 144.0, 141.8, 137.4, 135.0, 132.9, 131.6, 129.6, 129.3, 129.2, 128.0, 127.9, 127.7, 127.4, 127.2, 127.0, 126.7, 124.8, 124.3, 123.6, 21.3, 18.7; ESMS *m/z* 360 (MH^+).

3-Chloro-2,4-diphenylbenzo[*h*]quinoline 3c. mp 126-127 °C; ^1H NMR ($CDCl_3$) δ 7.3-8.0 (15H, m), 9.4 (1H, d, J = 7.5Hz); ^{13}C NMR ($CDCl_3$) δ 155.2, 147.0, 144.1, 139.5,

136.1, 133.1, 131.1, 130.0, 130.0, 129.5, 128.7, 128.5, 128.4, 128.3, 127.8, 127.5, 127.2, 127.0, 125.3, 124.9, 123.1; ESMS *m/z* 368, 366 (MH^+).

3-Chloro-2-phenyl-4-*p*-tolylbenzo[*h*]quinoline 3d. mp 156-157 °C; ^1H NMR ($CDCl_3$) δ 2.5 (3H, s), 7.3-8.0 (14H, m), 9.4 (1H, d, J = 7.5Hz); ^{13}C NMR ($CDCl_3$) δ 155.2, 147.1, 144.1, 139.6, 138.1, 133.2, 133.1, 131.2, 130.0, 129.4, 129.2, 128.7, 128.3, 128.2, 127.8, 127.8, 127.5, 127.1, 125.5, 125.0, 123.2, 21.4; ESMS *m/z* 382, 380 (MH^+).

3-Bromo-2,4-diphenylbenzo[*h*]quinoline 4e. mp 139-141 °C; ^1H NMR ($CDCl_3$) δ 7.3-8.0 (15H, m), 9.4 (1H, d, J = 7.5Hz); ^{13}C NMR ($CDCl_3$) δ 156.6, 149.3, 144.3, 140.9, 138.3, 133.0, 130.9, 129.7, 129.1, 128.4, 128.3, 128.2, 128.1, 127.6, 127.4, 127.2, 126.6, 125.3, 124.8, 123.2, 118.9; ESMS *m/z* 412, 410 (MH^+).

3-Bromo-2-phenyl-4-*p*-tolylbenzo[*h*]quinoline 4f. mp 142-144 °C; ^1H NMR ($CDCl_3$) δ 2.5 (3H, s), 7.3-7.9 (14H, m), 9.4 (1H, d, J = 7.5Hz); ^{13}C NMR ($CDCl_3$) δ 156.8, 149.6, 144.6, 141.2, 138.1, 135.5, 133.3, 131.2, 129.9, 129.2, 129.2, 128.5, 128.4, 128.3, 127.8, 127.6, 127.2, 125.7, 125.0, 123.5, 119.3, 21.4; ESMS *m/z* 426, 424 (MH^+).

2,4-Diphenylbenzo[*h*]quinoline 5e. mp 158-160 °C; ^1H NMR ($CDCl_3$) δ 7.4-7.8 (14H, m), 8.4 (2H, d, J = 7.5Hz), 9.6 (1H, d, J = 7.5Hz); ^{13}C NMR ($CDCl_3$) δ 154.6, 148.8, 146.5, 139.4, 138.5, 133.3, 131.7, 129.4, 129.0, 128.6, 128.4, 128.1, 127.8, 127.4, 127.2, 127.0, 126.7, 124.9, 123.0, 122.6, 119.2; ESMS *m/z* 332 (MH^+).

2-Phenyl-4-*p*-tolylbenzo[*h*]quinoline 5f. mp 163-165 °C; ^1H NMR ($CDCl_3$) δ 2.5 (3H, s), 7.0-7.9 (13H, m), 8.4 (2H, d, J = 7.5Hz), 9.6 (1H, d, J = 7.5Hz); ^{13}C NMR ($CDCl_3$) δ 154.8, 151.5, 149.0, 146.7, 139.7, 138.2, 135.8, 133.5, 132.0, 129.6, 129.3, 128.8, 128.2, 127.6, 127.4, 127.1, 126.8, 125.5, 125.2, 123.4, 123.0, 21.4; ESMS *m/z* 346 (MH^+).

3-Chloro-2,4-diphenylbenzo[*f*]quinoline 6g. mp 183-185 °C; ^1H NMR ($CDCl_3$) δ 7.1 (1H, t, J = 9.0Hz), 7.3-7.4 (3H, m), 7.4-7.6 (7H, m), 7.8-7.9 (3H, m), 7.9 (1H, d, J = 9.0Hz), 8.0 (1H, d, J = 9.0Hz); ^{13}C NMR ($CDCl_3$) δ 156.3, 147.2, 147.0, 140.0, 139.2, 133.3, 131.9, 129.6, 129.6, 129.6, 129.4, 128.8, 128.8, 128.8, 128.5, 128.3, 128.1, 127.8, 126.9, 126.1, 124.3; ESMS *m/z* 368, 366 (MH^+).

3-Methyl-2-phenyl-4-*p*-tolylbenzo[*f*]quinoline 6h. mp 140-142 °C; ^1H NMR ($CDCl_3$) δ 2.1 (3H, s), 2.5 (3H, s), 7.1 (1H, t, J = 7.8Hz), 7.2 (2H, d, J = 7.8Hz), 7.4-7.5 (7H, m), 7.7 (2H, m), 7.8 (1H, d, J = 8.4Hz), 7.9 (1H, d, J = 9.0Hz), 8.0 (1H, d, J = 9.0Hz);

^{13}C NMR ($CDCl_3$) δ 159.1, 148.3, 147.0, 141.4, 138.8, 137.6, 133.2, 130.7, 130.5, 130.1, 129.2, 129.0, 128.6, 128.4, 128.3, 128.3, 128.1, 127.8, 126.1, 125.5, 123.2, 21.5, 19.1; ESMS *m/z* 360 (MH^+).

3-Methyl-2,4-diphenylpyrido[3,4-*h*]quinoline 7i. mp 166-168 °C; ^{1}H NMR ($CDCl_3$) δ 2.3 (3H, s), 7.3-7.4 (2H, m), 7.4 (1H, d, J = 9.0Hz), 7.5-7.6 (6H, m), 7.7 (1H, d, J = 8.7Hz), 7.8 (2H, m), 8.8 (1H, d, J = 5.7Hz), 9.1 (1H, d, J = 5.7Hz), 9.2 (1H, d, J = 0.9Hz); ^{13}C NMR ($CDCl_3$) δ 159.3, 150.9, 148.5, 145.4, 142.4, 141.2, 137.5, 136.0, 129.5, 129.4, 129.2, 128.8, 128.3, 128.2, 128.1, 127.9, 126.1, 125.2, 124.9, 117.7, 19.0; ESMS *m/z* 347 (MH^+).

3-Chloro-2,4-diphenylnaphtho[3,2-*h*]quinoline 8j. mp 191-193 °C; ^{1}H NMR ($CDCl_3$) δ 7.2 (1H, d, J = 9.6Hz), 7.4 (2H, m), 7.5-7.6 (8H, m), 7.8 (1H, d, J = 9.3Hz), 8.0-8.1 (3H, m), 8.2 (1H, m), 8.3 (1H, s), 9.9 (1H, s); ^{13}C NMR ($CDCl_3$) δ 155.0, 147.0, 145.3, 139.6, 136.3, 133.0, 132.3, 131.2, 130.1, 129.6, 129.3, 129.2, 129.0, 128.8, 128.6, 128.4, 128.0, 127.8, 127.5, 126.5, 126.3, 126.0, 125.4, 124.7, 123.0; ESMS *m/z* 418, 416 (MH^+).

3-Chloro-2,4-diphenylnaphtho[3,2-*f*]quinoline 9k. mp 209-211 °C; ^{1}H NMR ($CDCl_3$) δ 7.3 (1H, d, J = 8.1Hz), 7.4-7.6 (7H, m), 7.7 (3H, m), 7.8 (1H, m), 7.9-8.0 (4H, m), 8.0 (1H, d, J = 9.3Hz), 8.3 (1H, s); ^{13}C NMR ($CDCl_3$) δ 156.0, 147.9, 147.1, 140.1, 139.2, 132.5, 131.4, 131.2, 131.0, 129.8, 129.6, 129.0, 128.9, 128.8, 128.8, 128.5, 128.5, 128.3, 128.1, 127.1, 127.1, 126.8, 126.6, 125.7, 124.7; ESMS *m/z* 418, 416 (MH^+).

ACKNOWLEDGMENTS

This work was supported by the Spanish DGICYT (PB94-0483) and the Universidad de La Rioja (UR96PYB10PCG). Two of us (C.Q.T. and E.A.) would like to thank the Ministerio de Educación y Ciencia (Spain) for a fellowship.

REFERENCES AND NOTES

1. (a) Kametani, T.; Kasai, H. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Scientific Publishing Co.: Amsterdam, 1989; Vol. 3, p 385. (b) Yates, F. S. In *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, UK, 1984; Vol. 2, p

511. (c) Sainsbury, M. In *Rodd's Chemistry of Carbon Compounds*, Coffey, S., Ed.; Elsevier Scientific Publishing Co.: Amsterdam, 1978; Part G, p 171.

2. For reviews of methods for the synthesis of quinoline derivatives see: (a) Jones, G. In reference 1a; p 395. (b) Campbell, N. In reference 1c; Part F, 1976, p 235. (c) Newkome, G. R.; Paudler, W. W. *Contemporary Heterocyclic Chemistry. Syntheses, Reactions, and Applications*, Wiley: New York, 1982; p 200 (d) Gilchrist, T. L. *Heterocyclic Chemistry*, 2nd ed.; Longman Scientific & Technical: Essex, UK, 1992; p 152. (e) Joule, J. A.; Mills, K.; Smith, G. F. *Heterocyclic Chemistry*, 3rd ed.; Chapman & Hall: London, 1995; p 120.
3. Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry and Biochemistry and the Role of Heterocycles in Science, Technology, Medicine and Agriculture*, Wiley: Chichester, UK, 1997. Gringauz, A. *Introduction to Medicinal Chemistry. How Drugs Act and Why*, Wiley: New York, 1997.
4. Campos, P. J.; Tan, C.-Q.; González, J. M.; Rodríguez, M. A. *Tetrahedron Lett.* **1993**, *34*, 5321.
5. Campos, P. J.; Tan, C.-Q.; Añón, E.; Rodríguez, M. A. *J. Org. Chem.* **1996**, *61*, 7195.
6. Hoberg, H.; Barluenga, J. *Synthesis* **1970**, 82. Barluenga, J.; Losada, C. P.; Olano, B. *Tetrahedron Lett.* **1993**, *34*, 5497.
7. Barluenga, J.; Tomás, M.; López-Ortiz, J. F.; Gotor, V. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2273.
8. Newhouse, B. J.; Bordner, J.; Augeri, D. J.; Litts, C. S.; Kleinman, E. F. *J. Org. Chem.* **1992**, *57*, 6991. Torii, S.; Xu, L. H.; Sadakane, M.; Okumoto, H. *Synlett* **1992**, 513.
9. By the contrary, irradiation of the debrominated alkene imine acylated at the imine group (see Scheme 2, R^1 = PhCO) for 10 h gave **5e** with good yield. Acylation was performed according to ref 10.
10. Barluenga, J.; Jardón, J.; Gotor, V. *J. Org. Chem.* **1985**, *50*, 802.
11. Párkányi, C.; Lee, Y. *Tetrahedron Lett.* **1974**, 1115.
12. Santamaria, J. In *Photoinduced Electron Transfer*; Fox, M.A.; Chanon, M., Eds.; Elsevier Scientific Publishing Co.: Amsterdam, 1992; Part B, p 483.
13. Laarhoven, W. H. In *Organic Photochemistry*, Padwa, A., Ed.; Marcel Dekker: New York, 1989; Vol. 10, p 163.