

FORMATION OF ISOQUINOLINE DERIVATIVES BY THE IRRADIATION OF *N*-ACETYL- α -DEHYDROPHENYLALANINE ETHYL ESTER AND ITS DERIVATIVES

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Abstract—The irradiation of a nitrogen-purged acetonitrile solution of the title compounds (**1**) with Pyrex filtered light was found to give isoquinoline derivatives (**2**) *via* the excited state (*Z*)-isomers, whereas in methanol 1-azetine derivative was also detected along with **2** but side reactions occurred appreciably on prolonged irradiation. An examination of substituent effects on the reactivities of the excited state (*Z*)-isomers shows that the efficiency for formation of **2** undergoes great steric and electronic effects of the substituent introduced into the benzene ring of **1**, though the bulkiness of the alkoxy carbonyl group in **1** affected this efficiency to only a slight extent. On the other hand, in the presence of benzophenone as a triplet sensitizer, the starting (*Z*)-isomer underwent an exclusive isomerization into the corresponding (*E*)-isomer without yielding any isoquinoline derivative, being consistent with the occurrence of the photocyclization reaction from the excited singlet state (*Z*)-isomer.

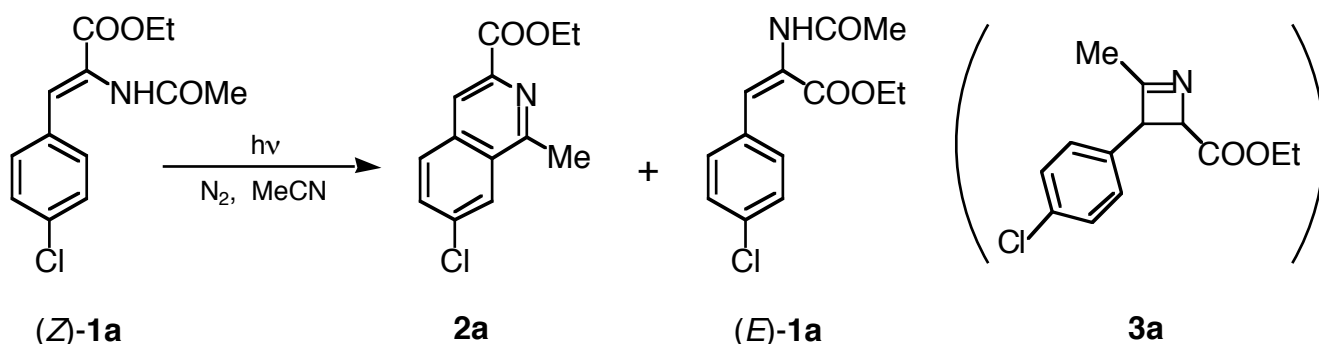
It is well-known that numerous biomolecules and natural products contain various types of heterocyclic compounds as their principal constituents. We have been interested in exploring the excited state reactivities of α -dehydroamino acid derivatives, one of the main constituents of some antibiotics,¹ as well as in developing these photochemical reactions of synthetic utility. Taking into account that α -dehydroamino acid derived products may possess high biological activities, we embarked on a systematic study regarding photochemical reactivities of aryl substituted α -dehydroalanine derivatives and discovered novel photocyclization reactions forming biochemically and pharmaceutically useful products.^{2,3} As an extension of the investigation into the photochemical processes of *N*-acetyl- α -dehydrophenylalanine derivatives [(*Z*)-2-acetylamino-*N*-butyl-3-(4-substituted phenyl)-2-propenamides],² we confined our attention to the characterization of the excited state reactivities of *N*-acetyl- α -dehydrophenylalanine ethyl ester [ethyl (*Z*)-2-acetylamino-3-(4-chlorophenyl)-2-propenoate, ((*Z*)-**1a**)] and its derivatives (**1b-i**). In this note we

present results that demonstrate that the photoreaction of **1** in MeCN gives isoquinoline derivatives without forming any 1-azetines, and that the composition for the former product undergoes dramatic effects of substituents on the benzene ring but the alkoxy carbonyl group exerts only a slight steric effect on this composition.



1a ($R^1 = \text{Cl}$, $R^2 = \text{H}$); **1b** ($R^1 = R^2 = \text{H}$); **1g** ($R^3 = \text{Me}$); **1h** ($R^3 = i\text{-Pr}$); **1i** ($R^3 = t\text{-Bu}$)
1c ($R^1 = \text{Me}$, $R^2 = \text{H}$); **1d** ($R^1 = \text{OMe}$, $R^2 = \text{H}$);
1e ($R^1 = \text{CF}_3$, $R^2 = \text{H}$); **1f** ($R^1 = R^2 = \text{Cl}$)

The starting (*Z*)-isomers (**1a–i**) were prepared in good yields by the ring opening reactions of aryl substituted oxazolones with alcohols in the presence of triethylamine.⁴ After a nitrogen purged MeCN solution of **1a** ($4.0 \times 10^{-3} \text{ mol dm}^{-3}$) was irradiated with Pyrex filtered light ($>280 \text{ nm}$) from a 400 W high pressure Hg lamp for 24 h at room temperature, the product mixture obtained was subjected to preparative thin layer chromatography over silica gel, which allowed us to isolate (*Z*)-**1a** (53%: isolated yield), (*E*)-**1a** (11%), and **2a** (12%). A careful ^1H NMR analysis of the product mixture indicated the negligible formation of the 1-azetine isomer (**3a**) (Scheme 1). Because 1-azetine derivatives are shown to be stable under the irradiation conditions employed,² it is very unlikely that **3a** once formed decomposes during irradiation.



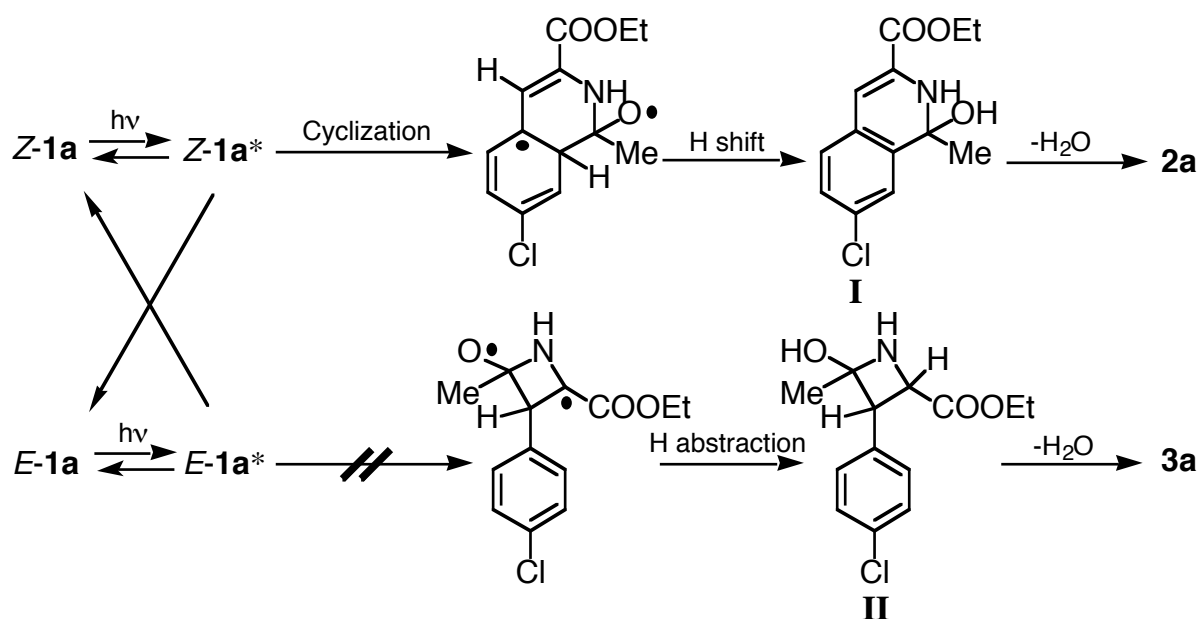
Scheme 1. Product distribution derived from the photoreaction of (*Z*)-**1a** in MeCN

The finding that the photoproduct (**2a**) is stable enough such that it undergoes only negligible decomposition under the irradiation conditions made it possible to monitor the reaction by means of ^1H NMR spectroscopy, as typically shown in Table 1. The result obtained for (*Z*)-**1a** demonstrates the rapid production of (*E*)-**1a** and the subsequent increase in a composition for **2a** with the decrease of (*Z*)-isomer

composition. In a previous study² it was strongly suggested that the isoquinoline is formed *via* cyclization process from the excited state (*Z*)-isomer while the cyclization reaction from the (*E*)-isomer is responsible for the appearance of 1-azetine derivative. In addition to Chem 3D modeling of (*Z*)-**1a** and (*E*)-**1a** which shows that the (*Z*)-isomer adopts a most suitable conformation for the cyclization affording **2a**, these considerations led us to propose Scheme 2 that explains the observed product distribution. We previously showed that the 24 h irradiation of *N*-acetyl- α -dehydrophenylalaninamide derivative [(*Z*)-2-acetylamino-*N*-butyl-3-(4-chlorophenyl)-2-propenamide] in MeCN affords isoquinoline (32%) and 1-azetine (*trans* + *cis*, 19%) derivatives along with (*Z*)- (33%) and (*E*)-isomers (16%).² A comparison of this result with the product composition obtained by the 24 h irradiation of (*Z*)-**1a** confirms that the replacement of butylaminocarbonyl group in the α -dehydrophenylalaninamide derivative by ethoxycarbonyl lowers the reactivity of the excited state (*Z*)-isomer.

Table 1. Relation between irradiation time and composition (%) of each compound in MeCN

Compound	Time/h						
	0	2	4	8	12	18	24
(<i>Z</i>)- 1a	100	83.9	80.3	77.8	73.5	70.8	69.0
(<i>E</i>)- 1a		14.3	15.8	15.0	14.6	13.9	12.7
2a		1.8	3.9	7.2	11.9	15.3	18.3



Scheme 2. Proposed mechanism for the formation of **2a**

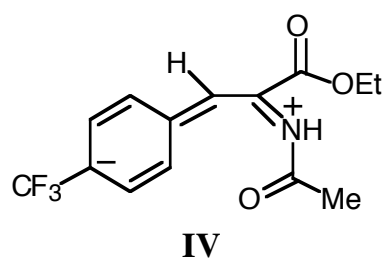
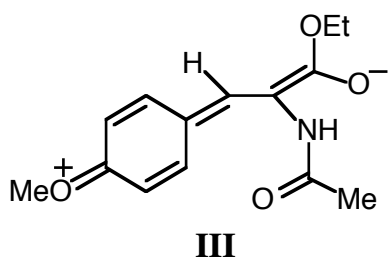
If we adopt this mechanism for the formation of the isoquinoline derivative (**2a**), we forced to explain the reason for the complete suppression of cyclization from the excited state (*E*)-isomer. Chem 3D modeling of **I** and **II** (Scheme 2), precursors of the isoquinoline (**2a**) and the 1-azetine (**3a**), respectively, shows that the distance between lone pairs of electrons on the ring nitrogen and the ethoxy oxygen is shorter in the latter precursor than in the former. It is, thus, very likely that there is much stronger electronic repulsion between the lone pairs of electrons in **II**, compared with **I**. This repulsion may greatly slow down the rate for the cyclization reaction of (*E*)-**1a** in the excited state to result in an exclusive deactivation of the (*E*)-isomer. Then, we expect that the hydrogen bonding solvation of the azetidene ring nitrogen by MeOH molecules weaken the electronic repulsion enabling the cyclization reaction from the excited state (*E*)-isomer to proceed. On irradiation of a MeOH solution of (*Z*)-**1a** for 12 h under the same conditions, there appeared substantial amounts of the *trans*-azetine isomer (**3a**) (about 5%, ¹H NMR analysis), whose ring proton signals with the $J_{3,4}$ value of 7.3 Hz were detected at 4.71 and 5.64 ppm (DMSO-*d*₆), along with **2a** (about 8%). This observation is consistent with our expectation, thus providing a piece of evidence in support of the interpretation described above. In MeOH having a great hydrogen bonding solvation ability, however, the undesirable side reactions occurred to a large extent on prolonged irradiation. The presence of byproducts and the relatively low stability of the 1-azetine isomer made it very difficult to isolate analytical grade **3a**.

In Table 2 are shown substituent effects on the product distribution and composition obtained for (*Z*)-**1a** in MeCN. Interestingly, the introduction of strong electron donating (OMe) and electron withdrawing (CF₃) groups at the *para* position on the benzene ring greatly reduces the composition for the isoquinoline derivative (**2a**), whereas this composition as well as the efficiency of the isomerization into (*E*)-**1a** undergoes only a minor stereoelectronic effect of the alkyl substituents. In addition, a comparison of the excited state reactivity of (*Z*)-**1a** with that of (*Z*)-**1f** reveals that the replacement of the *ortho* hydrogen on the benzene ring in **1a** by relatively bulky chlorine enhances the isomerization efficiency but completely suppresses the formation of the corresponding isoquinoline derivative. (*Z*)-**1a–f** in MeCN exhibit the first UV absorption bands at 281 (**1b**; molar absorption coefficient, $\epsilon_{\max} = 1.7 \times 10^4$), 286 (**1a**; $\epsilon_{\max} = 2.1 \times 10^4$), 288 (**1c**; $\epsilon_{\max} = 2.2 \times 10^4$), 303 (**1d**; $\epsilon_{\max} = 2.4 \times 10^4$), 284 (**1e**; $\epsilon_{\max} = 1.4 \times 10^4$), and 283 nm (**1f**; $\epsilon_{\max} = 1.6 \times 10^4$ dm³ mol⁻¹ cm⁻¹). A comparison of these UV spectral data confirms that the electron donating MeO substituent (**1d**) shifts the absorption band to longer wavelength (22 nm) with increasing its intensity, compared with the H (**1b**), whereas the absorption of **1b** is slightly red shifted (2 nm) with decreasing its intensity on introducing the electron withdrawing CF₃ group (**1e**) into **1b**. These findings strongly suggest a contribution of the resonance structures (**III**) and (**IV**) to the overall structures in the excited state. The relative rate for the deactivation of the excited state (*Z*)-isomer is considered to increase with an increase in the contribution of these resonance structures. On the other hand, MM2 calculations for the ground state conformation of **1a** and **1f** suggest that the introduction of an additional chlorine atom at the *ortho* position exerts a fairly large steric effect on the bond forming step between the acetyl carbonyl carbon and the phenyl *ortho* carbon of (*Z*)-**1f** in the excited state (Figure 1). This must be reflected in a lowering of the relative rate for the cyclization process. In addition, the increased relative rate for the isomerization into (*E*)-**1f** also further slows down the cyclization reaction to give a negligible amount of the isoquinoline

derivative (**2f**), as observed (Table 2).

Table 2. Substituent effects on the composition of each compound obtained by 2 and 24 h irradiations of the starting (*Z*)-**1a-i** (4.0×10^{-3} mol dm⁻³) in MeCN

Compound	Irradiation time/h	Composition (%)		
		(<i>Z</i>)- 1	(<i>E</i>)- 1	2
1a (R ¹ = Cl, R ² = H, R ³ = Et)	2	83.9	14.3	1.8
	24	65.8	15.9	18.3
1b (R ¹ = R ² = H, R ³ = Et)	2	80.0	18.6	1.4
	24	63.6	18.7	17.7
1c (R ¹ = Me, R ² = H, R ³ = Et)	2	81.0	17.5	1.5
	24	65.0	17.7	17.3
1d (R ¹ = OMe, R ² = H, R ³ = Et)	2	86.1	13.6	0.3
	24	81.6	14.7	3.7
1e (R ¹ = CF ₃ , R ² = H, R ³ = Et)	2	79.0	21.0	0
	24	76.1	21.0	2.9
1f (R ¹ = R ² = Cl, R ³ = Et)	2	75.0	25.0	0
	24	61.4	38.6	0
1g (R ¹ = Cl, R ² = H, R ³ = Me)	2	83.0	17.0	0
	24	73.0	16.2	11.8
1h (R ¹ = Cl, R ² = H, R ³ = <i>i</i> -Pr)	2	81.8	16.8	1.4
	24	69.6	16.0	14.4
1i (R ¹ = Cl, R ² = H, R ³ = <i>t</i> -Bu)	2	74.9	25.1	0
	24	67.6	20.0	12.4



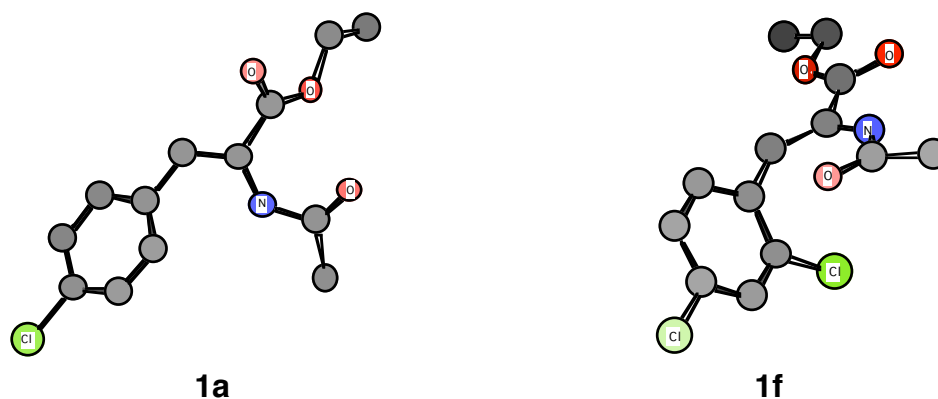


Figure 1. Energy-minimized conformations of **1a** and **1f**

It is an important issue to elucidate the spin multiplicity of the excited state from which the cyclization of **1** takes place forming isoquinoline derivatives. For this purpose we chose (*Z*)-**1a** as the starting material and benzophenone (BP) as a triplet sensitizer,^{5,6} and a nitrogen purged MeCN solution of (*Z*)-**1a** (4.0×10^{-3} mol dm⁻³) containing BP (4.0×10^{-2} mol dm⁻³) was irradiated at room temperature with light of wavelengths longer than 340 nm, which permitted selective excitation of the sensitizer. The fact that the room temperature phosphorescence of BP is quenched by (*Z*)-**1a** (2.0 – 8.0×10^{-4} mol dm⁻³) according to the Stern-Volmer equation, $I_0/I = 1 + 690[(Z)\text{-}1a]$, where I and I_0 refer to the phosphorescence intensities with and without **1a**, respectively, demonstrates that BP acts as a good triplet sensitizer. An inspection of Table 3 reveals that triplet BP accelerates only the isomerization without forming any isoquinoline derivative (**2a**). Because a ¹H NMR analysis of the reaction mixtures showed no sign of the appearance of BP derived product(s), this finding allows us to conclude that the photocyclization reaction of **1** proceeds preferentially through its excited singlet state and, hence, substantiates the involvement of the resonance structures (III) and (IV) in the excited singlet state (*Z*)-**1**.

Table 3. The composition of each compound obtained by the BP(4.0×10^{-2} mol dm⁻³)-sensitized reaction of (*Z*)-**1a** (4.0×10^{-3} mol dm⁻³) in nitrogen saturated MeCN

Irradiation time /h	Composition (%)		
	(<i>Z</i>)- 1a	(<i>E</i>)- 1a	2a
0	100	0	0
2	47.3	52.7	0
4	46.2	53.8	0
6	46.6	53.4	0
9	46.3	53.7	0

Although there are extensive synthetic routes to isoquinoline derivatives,⁷ convenient photochemical routes

to these derivatives are scarcely known.⁸ The procedure for preparing the starting **1** is very simple and is easily applicable to its related compounds. The photoreaction of substituted *N*-acetyl- α -dehydrophenylalanines described above, therefore, provides a synthetic method that enables us to obtain various kinds of isoquinoline derivatives without accompanying the appearance of 1-azetines.

EXPERIMENTAL

General

¹H and ¹³C NMR and IR spectra were taken with a JEOL JNM-A500 spectrometer and a Hitachi 270-30 infrared spectrometer, respectively. Chemical shifts were determined using tetramethylsilane as an internal standard. UV absorption spectra were recorded on a Shimadzu UV-2200 spectrophotometer. A cell with a 10 mm pathlength was used. The phosphorescence spectra of BP at rt were measured in the presence and absence of (*Z*)-**1a** under nitrogen with a Shimadzu RF-5000 spectrofluorimeter. The 366 nm light was used for the selective excitation of BP. MeOH and MeCN were purified according to the standard procedures⁹ and freshly distilled prior to use. All other reagents used were obtained from commercial sources and were of the highest grade available. MM2 calculations were accomplished by using the Mac SPARTAN *Plus* available from Wavefunction, Inc.

General Procedure for the Synthesis of (*Z*)-2-Methyl-4-(substituted benzylidene)-5(4*H*)-oxazolones. *N*-Acetylglycine (15.0 g, 0.13 mol), substituted benzaldehyde (0.15 mol) and sodium acetate (8.0 g, 0.10 mol) were added to acetic anhydride (150 mL) and the resulting mixture was heated at 70–85 °C for 1–2 h with stirring. The mixture was cooled with ice and then poured into ice-water (200 mL). The solid separated out was collected by filtration with suction and washed with small amounts of cold EtOH. After the crude product had been air-dried at rt, it was recrystallized from CHCl₃–hexane to give yellow crystals (60–73%).

(*Z*)-2-Methyl-4-(4-methoxybenzylidene)-5(4*H*)-oxazolone. mp 109.5–110.0 °C. IR (KBr): 1800, 1800, 1776, 1662, 1263 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 2.39 (3H, s), 3.87 (3H, s), 6.96 (2H, d, *J* = 8.5 Hz), 7.11 (1H, s), 8.06 (2H, d, *J* = 8.5 Hz).

(*Z*)-2-Methyl-4-(4-methylbenzylidene)-5(4*H*)-oxazolone. mp 135.0–136.0 °C. IR (KBr): 1809, 1776, 1656, 1266 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 2.38 (3H, s), 2.39 (3H, s), 7.11 (1H, s), 7.23 (2H, d, *J* = 8.3 Hz), 7.96 (2H, d, *J* = 8.3 Hz).

(*Z*)-2-Methyl-4-benzylidene-5(4*H*)-oxazolone. mp 152.0–152.5 °C. IR (KBr): 1779, 1659, 1266 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 2.38 (3H, s), 7.13 (1H, s), 7.39–7.44 (3H, m), 8.04–8.09 (2H, m).

(*Z*)-2-Methyl-4-(4-chlorobenzylidene)-5(4*H*)-oxazolone. mp 143.0–144.0 °C. IR (KBr):

1800, 1773, 1659, 1260 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 2.40 (3H, s), 7.05 (1H, s), 7.39 (2H, d, $J= 8.3$ Hz), 8.01 (2H, d, $J= 8.3$ Hz).

(Z)-2-Methyl-4-[4-(trifluoromethyl)benzylidene]-5(4H)-oxazolone. mp 110.0–112.0 $^\circ\text{C}$. IR (KBr): 1806, 1779, 1665, 1257 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 2.43 (3H, s), 7.12 (1H, s), 7.68 (2H, d, $J= 8.3$ Hz), 8.18 (2H, d, $J= 8.3$ Hz).

(Z)-2-Methyl-4-(2,4-dichlorobenzylidene)-5(4H)-oxazolone. mp 173.0–174.0 $^\circ\text{C}$. IR (KBr): 1809, 1785, 1656, 1266 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 2.42 (3H, s), 7.33 (1H, dd, $J= 2.0, 8.3$ Hz), 7.47 (1H, d, $J= 2.0$ Hz), 7.54 (1H, s), 8.67 (1H, d, $J= 8.3$ Hz).

General Procedure for the Synthesis of Alkyl (Z)-2-Acetylamino-3-(substituted phenyl)-2-propenoates [(Z)-1a–i]. (Z)-2-Methyl-4-(substituted benzylidene)-5(4H)-oxazolone (0.020 mol) was added to alcohol (200 mL) containing small amounts of triethylamine and the resulting solution was refluxed for 2–4 h. After removal of the solvent under reduced pressure, the solid residue obtained was recrystallized from CHCl_3 -hexane affording colorless crystals (60–70%).

Ethyl (Z)-2-Acetylamino-3-(4-chlorophenyl)-2-propenoate [(Z)-1a]. mp 152.0–153.0 $^\circ\text{C}$. IR (KBr): 3268, 1725, 1659, 1257 cm^{-1} . ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 1.24 (3H, t, $J= 7.0$ Hz), 2.00 (3H, s), 4.17 (2H, q, $J= 7.0$ Hz), 7.14 (1H, s), 7.47 (2H, d, $J= 8.6$ Hz), 7.64 (2H, d, $J= 8.6$ Hz), 9.62 (1H, s). ^{13}C NMR (125.7 MHz, $\text{DMSO}-d_6$): δ 14.0, 22.4, 60.8, 127.5, 128.6, 129.1, 131.3, 132.4, 133.6, 164.8, 169.3. Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{NO}_3\text{Cl}$: C, 58.33; H, 5.27; N, 5.23. Found: C, 58.28; H, 4.97; N, 4.96.

Ethyl (Z)-2-Acetylamino-3-phenyl-2-propenoate [(Z)-1b]. mp 99.5–100.0 $^\circ\text{C}$. IR (KBr): 3256, 1725, 1659, 1245 cm^{-1} . ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 1.23 (3H, t, $J= 7.0$ Hz), 1.99 (3H, s), 4.16 (2H, q, $J= 7.0$ Hz), 7.15 (1H, s), 7.36–7.43 (3H, m), 7.62 (2H, d, $J= 7.3$ Hz), 9.61 (1H, s). ^{13}C NMR (125.7 MHz, $\text{DMSO}-d_6$): δ 14.1, 22.4, 60.7, 126.9, 128.6, 129.2, 129.7, 130.7, 133.4, 164.9, 169.4. Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.82; H, 6.19; N, 5.89.

Ethyl (Z)-2-Acetylamino-3-(4-tolyl)-2-propenoate [(Z)-1c]. mp 142.0–144.0 $^\circ\text{C}$. IR (KBr): 3268, 1722, 1659, 1251 cm^{-1} . ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 1.23 (3H, t, $J= 7.0$ Hz), 1.99 (3H, s), 2.32 (3H, s), 4.15 (2H, q, $J= 7.0$ Hz), 7.14 (1H, s), 7.23 (2H, d, $J= 8.2$ Hz), 7.52 (2H, d, $J= 8.2$ Hz), 9.54 (1H, s). ^{13}C NMR (125.7 MHz, $\text{DMSO}-d_6$): δ 14.1, 20.9, 22.4, 60.7, 126.1, 129.2, 129.8, 130.6, 131.1, 139.1, 165.1, 169.3. Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.86; H, 6.63; N, 5.58.

Ethyl (Z)-2-Acetylamino-3-(4-methoxyphenyl)-2-propenoate [(Z)-1d]. mp 115.0–116.5 $^\circ\text{C}$. IR (KBr): 3274, 1722, 1662, 1251 cm^{-1} . ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 1.23 (3H, t, $J= 7.0$ Hz),

1.99 (3H, s), 3.79 (3H, s), 4.14 (2H, q, $J = 7.0$ Hz), 6.98 (2H, d, $J = 8.8$ Hz), 7.18 (1H, s), 7.61 (2H, d, $J = 8.8$ Hz), 9.48 (1H, s). ^{13}C NMR (125.7 MHz, DMSO- d_6): δ 14.1, 22.4, 55.3, 60.6, 114.3, 124.6, 125.9, 131.5, 131.7, 160.1, 165.2, 169.3. Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.57; H, 6.21; N, 5.26.

Ethyl (Z)-2-Acetylamino-3-[4-(trifluoromethyl)phenyl]-2-propenoate [(Z)-1e]. mp 121.0–122.0 °C. IR (KBr): 3322, 1740, 1677, 1260 cm^{-1} . ^1H NMR (500 MHz, DMSO- d_6): δ 1.25 (3H, t, $J = 7.2$ Hz), 2.00 (3H, s), 4.19 (2H, q, $J = 7.2$ Hz), 7.17 (1H, s), 7.76 (2H, d, $J = 8.2$ Hz), 7.80 (2H, d, $J = 8.2$ Hz), 9.74 (1H, s). ^{13}C NMR (125.7 MHz, DMSO- d_6): δ 13.9, 22.4, 60.9, 124.0 (q, $J = 272$ Hz), 125.3 (q, $J = 3$ Hz), 128.0, 128.7 (q, $J = 31$ Hz), 129.1, 130.1, 137.7, 164.7, 169.4. Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{NO}_3\text{F}_3$: C, 55.82; H, 4.68; N, 4.65. Found: C, 55.91; H, 4.41; N, 4.58.

Ethyl (Z)-2-Acetylamino-3-(2,4-dichlorophenyl)-2-propenoate [(Z)-1f]. mp 126.0–127.0 °C. IR (KBr): 3238, 1722, 1662, 1278 cm^{-1} . ^1H NMR (500 MHz, DMSO- d_6): δ 1.24 (3H, t, $J = 7.0$ Hz), 1.93 (3H, s), 4.19 (2H, q, $J = 7.0$ Hz), 7.08 (1H, s), 7.47 (1H, dd, $J = 2.1, 8.5$ Hz), 7.61 (1H, d, $J = 8.5$ Hz), 7.72 (1H, d, $J = 2.1$ Hz), 9.64 (1H, s). ^{13}C NMR (125.7 MHz, DMSO- d_6): δ 13.9, 22.3, 61.0, 123.7, 127.4, 128.9, 129.6, 130.9, 131.1, 133.8, 134.0, 164.3, 169.1. Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_3\text{Cl}_2$: C, 51.68; H, 4.34; N, 4.64. Found: C, 51.68; H, 3.96; N, 4.62.

Methyl (Z)-2-Acetylamino-3-(4-chlorophenyl)-2-propenoate [(Z)-1g]. mp 155.0–156.0 °C. IR (KBr): 3214, 1734, 1668, 1248 cm^{-1} . ^1H NMR (500 MHz, DMSO- d_6): δ 2.00 (3H, s), 3.71 (3H, s), 7.16 (1H, s), 7.48 (2H, d, $J = 8.5$ Hz), 7.64 (2H, d, $J = 8.5$ Hz), 9.65 (1H, s). ^{13}C NMR (125.7 MHz, DMSO- d_6): δ 22.4, 52.2, 127.2, 128.6, 129.6, 131.4, 132.3, 133.7, 165.4, 169.4. Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{NO}_3\text{Cl}$: C, 56.82; H, 4.77; N, 5.52. Found: C, 56.82; H, 4.65; N, 5.38.

Isopropyl (Z)-2-Acetylamino-3-(4-chlorophenyl)-2-propenoate [(Z)-1h]. mp 143.0–144.0 °C. IR (KBr): 3238, 1713, 1668, 1263 cm^{-1} . ^1H NMR (500 MHz, DMSO- d_6): δ 1.23 (6H, d, $J = 6.1$ Hz), 1.99 (3H, s), 4.96 (1H, q, $J = 6.1$ Hz), 7.09 (1H, s), 7.47 (2H, d, $J = 8.5$ Hz), 7.64 (2H, d, $J = 8.5$ Hz), 9.60 (1H, s). ^{13}C NMR (125.7 MHz, DMSO- d_6): δ 21.5, 22.4, 68.3, 128.0, 128.6, 128.7, 131.3, 132.4, 133.5, 164.4, 169.3. Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_3\text{Cl}$: C, 59.68; H, 5.72; N, 4.97. Found: C, 59.85; H, 5.82; N, 5.12.

tert-Butyl (Z)-2-Acetylamino-3-(4-chlorophenyl)-2-propenoate [(Z)-1i]. mp 118.0–119.0 °C. IR (KBr): 3226, 1725, 1659, 1260 cm^{-1} . ^1H NMR (500 MHz, DMSO- d_6): δ 1.45 (9H, s), 1.98 (3H, s), 7.04 (1H, s), 7.46 (2H, d, $J = 8.5$ Hz), 7.61 (2H, d, $J = 8.5$ Hz), 9.53 (1H, s). ^{13}C NMR (125.7 MHz, DMSO- d_6): δ 22.3, 27.5, 80.5, 128.2, 128.5, 128.7, 131.2, 132.6, 133.3, 163.9, 169.2. Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{NO}_3\text{Cl}$: C, 60.91; H, 6.13; N, 4.74. Found: C, 60.97; H, 5.86; N, 4.35.

General Procedure for the Irradiation of (Z)-1a–i. A solution of (Z)-1 (4.0×10^{-3} mol dm^{-3}) in

MeCN (500 mL), placed in a Pyrex vessel, was irradiated for a given period of time under nitrogen with Pyrex-filtered light from a 400 W high pressure Hg lamp at rt. At regular time intervals, an appropriate amount of the solution (5 mL) being irradiated was pipetted off and concentrated to dryness *in vacuo* giving the residue which was subjected to ^1H NMR analysis in DMSO- d_6 . The composition was estimated from the area ratio of a given ^1H NMR signal for each compound. After 24 h irradiation, the remaining solution was concentrated to dryness under reduced pressure and the resulting residue was subjected to column chromatography over silica gel (230 mesh, Merck) eluting with EtOAc-hexane. For the purpose of isolating and purifying the photoproducts, preparative TLC plate (silica gel) was also used. Physical and spectroscopic properties of the isolated isomers ((*E*)-**1a-i**) and isoquinolines (**2a-e**) and (**2g-i**) are as follows.

(E)-1a. Oily liquid. IR (neat): 3310, 1719, 1635, 1245 cm^{-1} . ^1H NMR (500 MHz, DMSO- d_6): δ 1.08 (3H, t, $J= 7.3$ Hz), 1.95 (3H, s), 4.08 (2H, q, $J= 7.3$ Hz), 6.51 (1H, s), 7.29 (2H, d, $J= 8.6$ Hz), 7.38 (2H, d, $J= 8.6$ Hz), 10.05 (1H, s). ^{13}C NMR (125.7 MHz, DMSO- d_6): δ 13.4, 22.3, 60.6, 117.4, 128.2, 129.5, 130.1, 131.8, 133.2, 164.4, 168.0. Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{NO}_3\text{Cl}$: C, 58.33; H, 5.27; N, 5.23. Found: C, 58.33; H, 5.30; N, 5.00.

(E)-1b. Oily liquid. IR (neat): 3280, 1725, 1635, 1245 cm^{-1} . ^1H NMR (500 MHz, DMSO- d_6): δ 1.06 (3H, t, $J= 7.3$ Hz), 1.95 (3H, s), 4.07 (2H, q, $J= 7.3$ Hz), 6.52 (1H, s), 7.19 (2H, d, $J= 7.3$ Hz), 7.25 (1H, d, $J= 7.3$ Hz), 7.32 (2H, dd, $J= 7.3, 7.3$ Hz), 10.01 (1H, s). ^{13}C NMR (125.7 MHz, DMSO- d_6): δ 13.4, 22.4, 60.5, 118.8, 127.3, 127.8, 128.2, 129.5, 134.2, 164.6, 168.0. Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.88; H, 6.64; N, 6.00.

(E)-1c. Oily liquid. IR (neat): 3280, 1725, 1662, 1245 cm^{-1} . ^1H NMR (500 MHz, DMSO- d_6): δ 1.08 (3H, t, $J= 7.3$ Hz), 1.94 (3H, s), 2.28 (3H, s), 4.07 (2H, q, $J= 7.0$ Hz), 6.46 (1H, s), 7.09 (2H, d, $J= 8.2$ Hz), 7.12 (2H, d, $J= 8.2$ Hz), 9.97 (1H, s). ^{13}C NMR (125.7 MHz, DMSO- d_6): δ 13.5, 20.7, 22.4, 60.5, 119.1, 127.9, 128.7, 128.8, 131.3, 136.8, 164.8, 168.0. Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.05; H, 7.12; N, 5.58.

(E)-1d. Oily liquid. IR (neat): 3284, 1732, 1666, 1258 cm^{-1} . ^1H NMR (500 MHz, DMSO- d_6): δ 1.10 (3H, t, $J= 7.3$ Hz), 1.93 (3H, s), 3.75 (3H, s), 4.08 (2H, q, $J= 7.3$ Hz), 6.45 (1H, s), 6.88 (2H, d, $J= 8.5$ Hz), 7.15 (2H, d, $J= 8.5$ Hz), 9.91 (1H, s). ^{13}C NMR (125.7 MHz, DMSO- d_6): δ 13.6, 22.3, 55.1, 60.4, 113.7, 119.7, 126.5, 127.7, 129.4, 158.7, 164.9, 168.0. Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.59; H, 6.64; N, 5.64.

(E)-1e. mp 98.5–99.0 $^{\circ}\text{C}$. IR (KBr): 3322, 1740, 1677, 1260 cm^{-1} . ^1H NMR (500 MHz, DMSO- d_6): δ 1.06 (3H, t, $J= 7.3$ Hz), 1.98 (3H, s), 4.09 (2H, q, $J= 7.3$ Hz), 6.62 (1H, s), 7.40 (2H, d, $J= 7.9$ Hz), 7.65 (2H, d, $J= 7.9$ Hz), 10.15 (1H, s). ^{13}C NMR (125.7 MHz, DMSO- d_6): δ 13.3, 22.4, 60.8, 116.5, 124.2 (q, $J= 271$ Hz), 125.0 (q, $J= 4$ Hz), 127.4 (q, $J= 31$ Hz), 128.4, 131.4, 138.7, 164.2,

168.1. Anal. Calcd for $C_{14}H_{14}NO_3F_3$: C, 55.82; H, 4.68; N, 4.65. Found: C, 56.01; H, 4.56; N, 4.25.

(E)-1f. mp 100.0–101.0 °C. IR (KBr): 3322, 1695, 1626, 1254 cm^{-1} . 1H NMR (500 MHz, DMSO- d_6): δ 1.01 (3H, t, $J= 7.0$ Hz), 1.99 (3H, s), 4.02 (2H, q, $J= 7.0$ Hz), 6.68 (1H, s), 7.20 (1H, d, $J= 8.2$ Hz), 7.39 (1H, dd, $J= 1.8, 8.2$ Hz), 7.65 (1H, d, $J= 1.8$ Hz), 10.13 (1H, s). ^{13}C NMR (125.7 MHz, DMSO- d_6): δ 13.4, 22.5, 60.7, 114.4, 127.1, 128.6, 130.6, 131.8, 132.2, 132.6, 133.1, 163.7, 168.3. Anal. Calcd for $C_{13}H_{13}NO_3Cl_2$: C, 51.68; H, 4.34; N, 4.64. Found: C, 51.45; H, 4.20; N, 4.49.

(E)-1g. mp 99.0–100.0 °C. IR (KBr): 3250, 1731, 1662, 1245 cm^{-1} . 1H NMR (500 MHz, DMSO- d_6): δ 1.96 (3H, s), 3.61 (3H, s), 6.50 (1H, s), 7.20 (2H, d, $J= 8.6$ Hz), 7.38 (2H, d, $J= 8.6$ Hz), 10.10 (1H, s). ^{13}C NMR (125.7 MHz, DMSO- d_6): δ 22.3, 51.8, 117.4, 128.3, 129.4, 129.7, 131.9, 133.1, 165.0, 168.1. Anal. Calcd for $C_{12}H_{12}NO_3Cl$: C, 56.82; H, 4.77; N, 5.52. Found: C, 56.76; H, 4.99; N, 5.21.

(E)-1h. mp 73.0–74.0 °C. IR (KBr): 3340, 1722, 1638, 1254 cm^{-1} . 1H NMR (500 MHz, DMSO- d_6): δ 1.08 (6H, d, $J= 6.1$ Hz), 1.95 (3H, s), 4.92 (1H, q, $J= 6.1$ Hz), 6.47 (1H, s), 7.21 (2H, d, $J= 8.6$ Hz), 7.38 (2H, d, $J= 8.6$ Hz), 10.02 (1H, s). ^{13}C NMR (125.7 MHz, DMSO- d_6): δ 21.0, 22.3, 68.2, 116.8, 128.2, 129.6, 130.6, 131.7, 133.3, 163.9, 168.0. Anal. Calcd for $C_{14}H_{16}NO_3Cl$: C, 59.68; H, 5.72; N, 4.97. Found: C, 59.73; H, 5.39; N, 4.57.

(E)-1i. mp 119.0–120.0 °C. IR (KBr): 3256, 1731, 1668, 1281 cm^{-1} . 1H NMR (500 MHz, DMSO- d_6): δ 1.32 (9H, s), 1.95 (3H, s), 6.49 (1H, s), 7.31 (2H, d, $J= 8.6$ Hz), 7.38 (2H, d, $J= 8.6$ Hz), 9.90 (1H, s). ^{13}C NMR (125.7 MHz, DMSO- d_6): δ 22.4, 27.3, 81.2, 117.1, 128.0, 129.8, 131.5, 131.7, 133.7, 163.1, 168.0. Anal. Calcd for $C_{15}H_{18}NO_3Cl$: C, 60.91; H, 6.13; N, 4.74. Found: C, 60.65; H, 5.87; N, 4.55.

Ethyl 7-Chloro-1-methylisoquinoline-3-carboxylate (2a). mp 98.5–100.5 °C. IR (KBr): 1731, 1278, 1233 cm^{-1} . 1H NMR (500 MHz, DMSO- d_6): δ 1.37 (3H, t, $J= 7.2$ Hz), 2.93 (3H, s), 4.39 (2H, q, $J= 7.2$ Hz), 7.90 (1H, dd, $J= 2.1, 8.9$ Hz), 8.24 (1H, d, $J= 8.9$ Hz), 8.37 (1H, br s), 8.51 (1H, s). ^{13}C NMR (125.7 MHz, DMSO- d_6): δ 14.2, 22.1, 60.9, 121.8, 124.9, 128.8, 130.9, 131.5, 133.6, 134.1, 140.5, 158.4, 164.9. Anal. Calcd for $C_{13}H_{12}NO_2Cl$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.55; H, 4.84; N, 5.38.

Ethyl 1-Methylisoquinoline-3-carboxylate (2b). mp 100.5–102.0 °C. IR (KBr): 1731, 1287, 1242 cm^{-1} . 1H NMR (500 MHz, DMSO- d_6): δ 1.37 (3H, t, $J= 7.0$ Hz), 2.94 (3H, s), 4.39 (2H, q, $J= 7.0$ Hz), 7.83 (1H, dd, $J= 7.0, 7.9$ Hz), 7.88 (1H, dd, $J= 7.0, 7.9$ Hz), 8.19 (1H, d, $J= 7.9$ Hz), 8.31 (1H, d, $J= 7.9$ Hz), 8.49 (1H, s). ^{13}C NMR (125.7 MHz, DMSO- d_6): δ 14.2, 22.1, 60.9, 122.2, 125.8, 128.1, 128.7, 129.7, 130.9, 135.0, 140.1, 158.8, 169.4. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.57; H, 6.03; N, 6.56.

Ethyl 7-Methyl-1-methylisoquinoline-3-carboxylate (2c). mp 93.5–94.0 °C. IR (KBr): 1731, 1287, 1242 cm^{-1} . ^1H NMR (500 MHz, $\text{DMSO-}d_6$): δ 1.37 (3H, t, $J= 6.1$ Hz), 2.58 (3H, s), 2.91 (3H, s), 4.38 (2H, q, $J= 6.1$ Hz), 7.71 (1H, d, $J= 7.6$ Hz), 8.07 (1H, d, $J= 7.6$ Hz), 8.07 (1H, br s), 8.42 (1H, s). ^{13}C NMR (125.7 MHz, $\text{DMSO-}d_6$): δ 14.3, 21.7, 22.1, 60.8, 122.1, 124.7, 128.3, 128.5, 132.9, 133.1, 139.4, 139.8, 158.0, 165.3. Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.05; H, 6.63; N, 6.00.

Ethyl 7-Methoxy-1-methylisoquinoline-3-carboxylate (2d). mp 115.0–116.0 °C. IR (KBr): 1728, 1699, 1290, 1254 cm^{-1} . ^1H NMR (500 MHz, $\text{DMSO-}d_6$): δ 1.36 (3H, t, $J= 7.3$ Hz), 2.91 (3H, s), 3.99 (3H, s), 4.37 (2H, q, $J= 7.3$ Hz), 7.51 (1H, d, $J= 8.6$ Hz), 7.52 (1H, br s), 8.11 (1H, d, $J= 8.6$ Hz), 8.42 (1H, s). ^{13}C NMR (125.7 MHz, $\text{DMSO-}d_6$): δ 14.3, 22.2, 55.7, 60.6, 104.4, 122.0, 123.0, 129.7, 130.1, 130.4, 138.2, 157.0, 159.9, 165.3. Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.48; H, 6.34; N, 5.89.

Ethyl 7-Trifluoromethyl-1-methylisoquinoline-3-carboxylate (2e). mp 91.0–92.5 °C. IR (KBr): 1743, 1716, 1284, 1242 cm^{-1} . ^1H NMR (500 MHz, $\text{DMSO-}d_6$): δ 1.38 (3H, t, $J= 6.7$ Hz), 3.03 (3H, s), 4.41 (2H, q, $J= 6.7$ Hz), 8.14 (1H, dd, $J= 1.2, 8.5$ Hz), 8.43 (1H, d, $J= 8.5$ Hz), 8.60 (1H, s), 8.64 (1H, br s). ^{13}C NMR (125.7 MHz, $\text{DMSO-}d_6$): δ 14.2, 22.2, 61.2, 121.7, 123.8, 126.0 (q, $J= 272$ Hz), 126.2 (q, $J= 3$ Hz), 127.2, 129.2 (q, $J= 32$ Hz), 130.6, 136.9, 142.1, 160.3, 164.9. Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{NO}_2\text{F}_3$: C, 59.37; H, 4.27; N, 4.95. Found: C, 59.54; H, 4.13; N, 4.67.

Methyl 7-Chloro-1-methylisoquinoline-3-carboxylate (2g). mp 125.0–126.0 °C. IR (KBr): 1716, 1284, 1236 cm^{-1} . ^1H NMR (500 MHz, $\text{DMSO-}d_6$): δ 2.93 (3H, s), 3.92 (3H, s), 7.91 (1H, dd, $J= 2.4, 8.6$ Hz), 8.24 (1H, d, $J= 8.6$ Hz), 8.37 (1H, br s), 8.53 (1H, s). ^{13}C NMR (125.7 MHz, $\text{DMSO-}d_6$): δ 22.1, 52.2, 121.9, 124.9, 128.8, 130.9, 131.5, 133.5, 134.1, 140.2, 158.3, 165.4. Anal. Calcd for $\text{C}_{12}\text{H}_{10}\text{NO}_2\text{Cl}$: C, 61.16; H, 4.28; N, 5.94. Found: C, 60.79; H, 4.51; N, 5.62.

Isopropyl 7-Chloro-1-methylisoquinoline-3-carboxylate (2h). mp 100.0–101.0 °C. IR (KBr): 1706, 1284, 1244 cm^{-1} . ^1H NMR (500 MHz, $\text{DMSO-}d_6$): δ 1.38 (6H, d, $J= 6.4$ Hz), 2.93 (3H, s), 5.22 (1H, q, $J= 6.4$ Hz), 7.89 (1H, dd, $J= 2.1, 8.5$ Hz), 8.23 (1H, d, $J= 8.5$ Hz), 8.35 (1H, d, $J= 2.1$ Hz), 8.47 (1H, s). ^{13}C NMR (125.7 MHz, $\text{DMSO-}d_6$): δ 21.7, 22.1, 68.5, 121.7, 124.9, 128.7, 130.9, 131.4, 133.5, 134.0, 140.8, 158.3, 164.4. Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{NO}_2\text{Cl}$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.62; H, 5.18; N, 5.27.

***tert*-Butyl 7-Chloro-1-methylisoquinoline-3-carboxylate (2i).** mp 91.0–92.0 °C. IR (KBr): 1704, 1287, 1248 cm^{-1} . ^1H NMR (500 MHz, $\text{DMSO-}d_6$): δ 1.60 (9H, s), 2.92 (3H, s), 7.88 (1H, dd, $J= 2.4, 9.2$ Hz), 8.21 (1H, d, $J= 9.2$ Hz), 8.35 (1H, br s), 8.41 (1H, s). ^{13}C NMR (125.7 MHz, $\text{DMSO-}d_6$): δ 22.2, 27.8, 81.1, 121.4, 125.0, 128.7, 130.9, 131.4, 133.6, 133.9, 141.7, 158.2, 164.1. Anal.

Calcd for C₁₅H₁₆NO₂Cl: C, 64.87; H, 5.81; N, 5.04. Found: C, 64.63; H, 5.87; N, 4.92.

***trans*-2-Methyl-3-(4-chlorophenyl)-4-ethoxycarbonyl-1-azetine (*trans*-3a).** We succeeded in isolating *trans*-3a (oily liquid) whose IR, ¹H, and ¹³C NMR spectra were consistent with the proposed structure, although the *trans*-isomer was contaminated with small amounts of by-product(s) and/or the azetine derived decomposition product(s). IR (neat): 3323, 1744, 1666, 1260, 1224 cm⁻¹. ¹H NMR (500 MHz; DMSO-*d*₆): δ 1.21 (3H, t, *J*= 7.3 Hz), 2.06 (3H, d, *J*= 1.2 Hz), 4.17 (2H, q, *J*= 7.3 Hz), 4.71 (1H, dd, *J*= 1.2, 7.3 Hz), 5.64 (1H, d, *J*= 7.3 Hz), 7.36 (2H, d, *J*= 8.5 Hz), 7.48 (2H, d, *J*= 8.5 Hz). ¹³C NMR (125.7 MHz, DMSO-*d*₆): δ 13.4, 13.9, 61.1, 75.8, 81.5, 127.6, 128.8, 133.0, 138.6, 165.7, 170.3.

Sensitization Effects on the Photoreactivity of (Z)-1a. For the purpose of examining sensitization effects on the product distribution and composition, an MeCN solution (40 mL) of (Z)-1a (4.0 × 10⁻³ mol dm⁻³) containing BP (4.0 × 10⁻² mol dm⁻³), placed in a Pyrex vessel, was irradiated under nitrogen at rt with light of wavelengths longer than 340 nm (Corning 0-52 glass filter) from a 450 W high pressure Hg lamp. At suitable time intervals, an aliquot (5 mL) of the solution was pipetted off and concentrated to dryness *in vacuo*. The resulting residue was dissolved in DMSO-*d*₆ and subjected to ¹H NMR analysis.

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