NOVEL 1, 3- SPIROCYCLIZATION REACTION IN THE PHOTOCHEMISTRY OF ANTHRANILIC ACID DERIVATIVES IN ACETONITRILE

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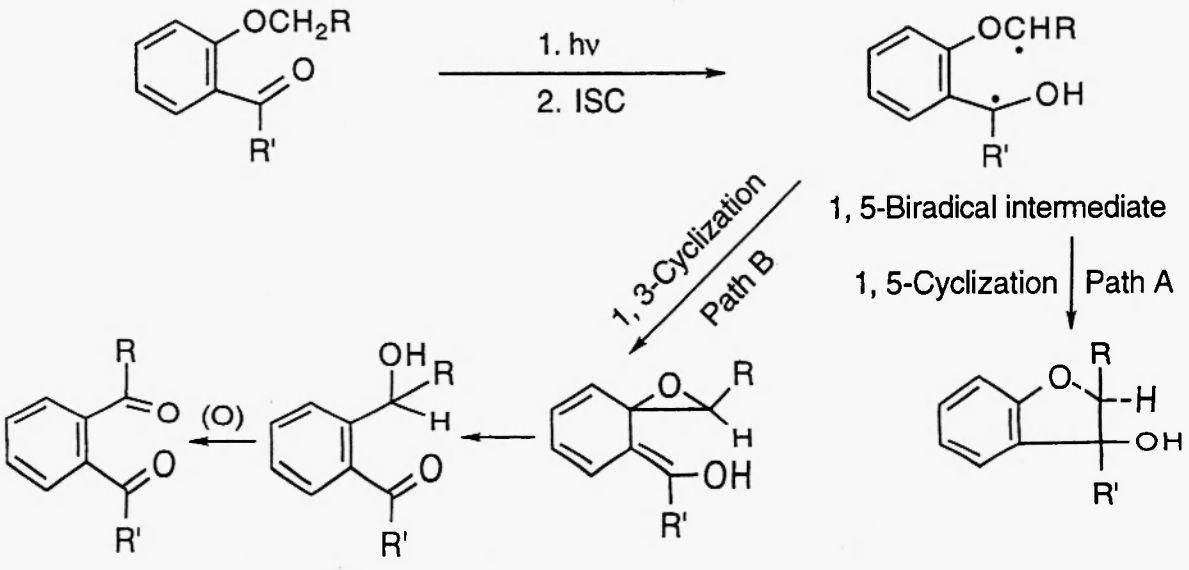
Abstract: Anthranilic acid derivatives **1a-c** were irradiated in acetonitrile solution to give imines (rearranged products) **2a-c** in each case. In the case of **1c**, a diastereomeric mixture of *dl*- and *meso*-dibenzoate derivative (dimerization product) **3c** was also obtained. The structures of the isolated products *via* photochemical reactions were confirmed by spectral methods. Substituent effects on the photochemistry of the reaction and reaction pathways were also discussed. The impossibility to obtain indole derivatives **8** during photolysis reactions of anthranilic acids **1a-c** were attributed to the instability of the formed 1, 5-biradical intermediate **5** formed by δ-hydrogen abstraction.

Introduction

Aromatic carbonyl compounds such as 2'-alkoxyacetophenones[1-6] and 2-alkoxybenzophenones[3, 5, 7-14] undergo photoinduced intramolecular hydrogen abstraction. In general, Photocyclization reactions of carbonyl compounds proceed *via* 1, 5-biradical intermediates formed through δ-hydrogen abstraction by the excited carbonyl group[3, 5, 7-9, 11] as shown in scheme 1.

Scheme 1



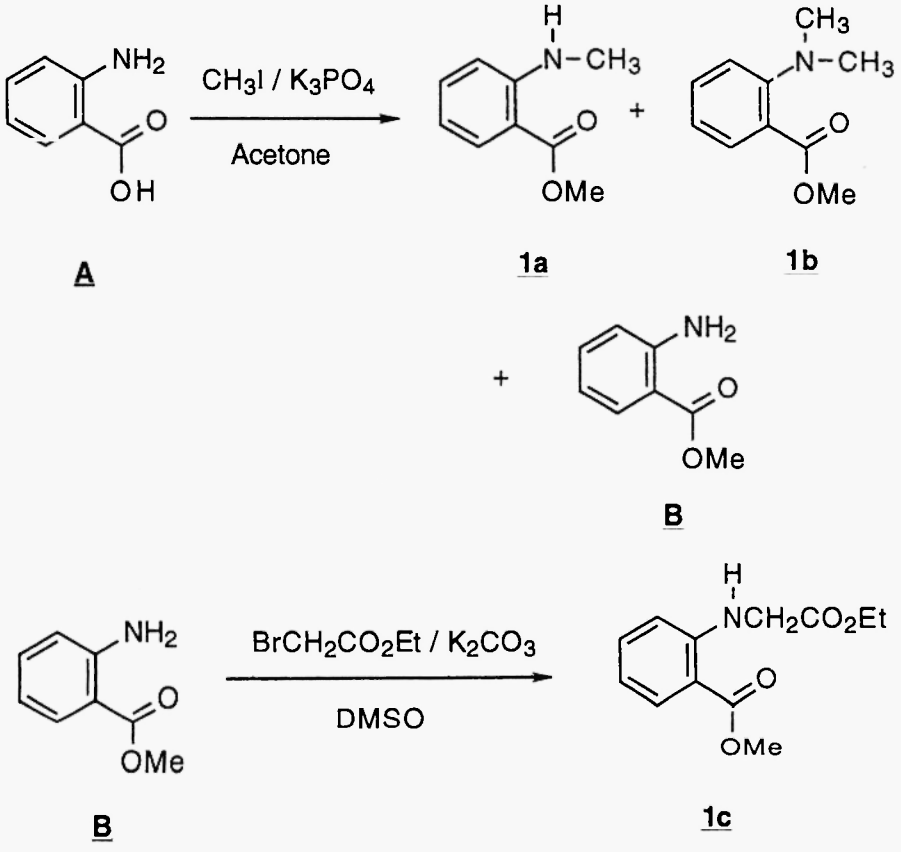
The 1, 5-biradicales can undergo two competing reactions. 1, 5-Cyclization to give heterocyclic compounds such as benzofurans (path A) or 1,3-cyclization to spiroenol (path B) [1, 3, 5] which rearrange to afford the corresponding rearranged products. Preference for path A or path B depends on the type of starting materials and the type of subsituents R and R'. For example, when benzophenones (R' = Ph) are used as starting materials, 1, 5-cyclization occurs to give dihydrobenzofuranols[3, 5]. In contrast, when bezaldehydes (R' = H) and acetophenones (R' = Me) are employed, 1, 3-cyclization competes with 1, 5-cyclization to afford a rearranged products[1].

For these reasons, we studied the photochemistry of anthranilic acid derivatives to show the effect of substituents on changing the reaction pathways.

Results and Discussion

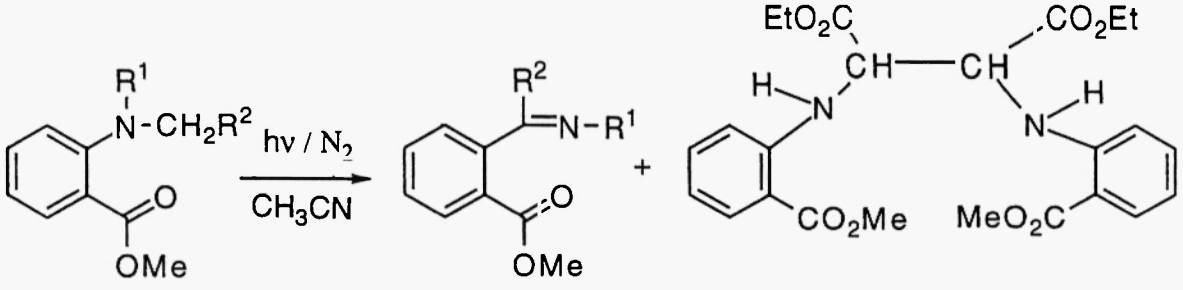
Starting materials **1a-b** for photoreactions such as methyl N-methylanthranilate, methyl N, N-dimethylanthranilate were prepared by the reaction of anthranilic acid **A** with methyl iodide in presence of tripotassium phosphate as a base. Ethyl N-(2-methoxycarbonyl-phenyl)glycine ester **1c** was prepared by the reaction of methyl anthranilate **B** with ethyl bromoacetate in presence of potassium carbonate as a base. The sequence of the reactions are outlined in Scheme 2.

Scheme 2



Initially, photocyclization reactions on anthranilic acid derivatives **1a-c** were performed with 400-W high-pressure mercury lamp (Pyrex filter) in acetonitrile. The results are outlined in Scheme 3 and Table 1.

Scheme 3



1a: $R^1 = R^2 = H$ **2a**: $R^1 = R^2 = H$

1b: $R^1 = CH_3$, $R^2 = H$ **2b**: $R^1 = CH_3$, $R^2 = H$ **3c**

1c: R^1 =H, $R^2 = CO_2Et$ **2c**: R^1 = H, $R^2 = CO_2Et$

Table 1

Photoreactions of Anthranilic Esters 1a-c [a].

Starting material	R^1	R^2	Irradiation time (minutes)	Conversion (%)	Product yield (%) [b] 2 [c]	3
1a	H	Me	185	70	72	0
1b	Me	Me	177	63	63	0
1c	H	CH_2CO_2Et	180	67	43	21[d]

[a] An acetonitrile solution (500 ml) of **1a-c** (2.00 mmoles) was irradiated after deoxygenation by bubbling nitrogen gas for 1 hour. [b] Yields based on reacted starting materials. [c] The stereochemistry of imines **2a-c** were not identified [d] a diastereomeric mixture of *dl*- and *meso*-dibenzoate **3c** was isolated and the ratio between the two isomer was 1: 1.

Photoreaction of methyl N-methylanhranilate **1a** in acetonitrile furnished N-2-methoxycarbonylbenzylideneamine (rearranged product) **2a** in 72% yield. The ^1H NMR spectrum reveals the presence of the azomethine proton as a singlet equivalent to one proton at 8.52 ppm. This high deshielding value confirm the imine structure for **2a**. ^{13}C NMR indicates also the azomethine carbon as a doublet at 159.5 ppm. These observations is in accordance to the IR spectra which shows a C=N and NH stretching vibrations at 1610 and 3300 cm^{-1}, respectively (see experimental section).

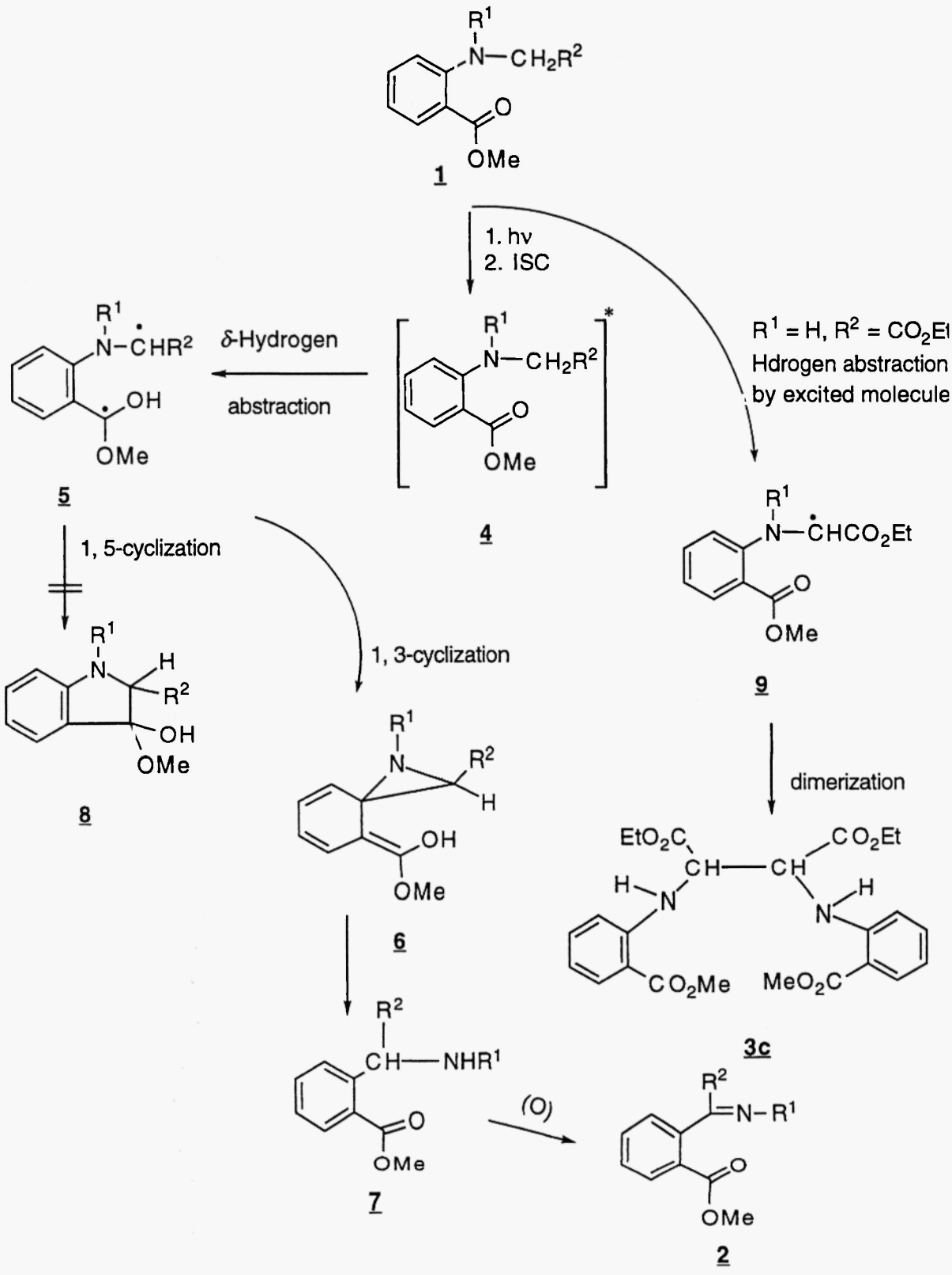
In the case of **1b**, N-(2-methoxycarbonyl-benzylidene)methylamine **2b** was produced in 63% yield. ^{1}H NMR and ^{13}C NMR confirm the imine structure for **2b** by the appearance of the azomethine hydrogen and carbon at 8.54 and 159.5 ppm, respectively. When **1c** (R^2 = CO_2Et) was irradiated, imine **2c** (43%) and a dibenzoate derivative **3c** (21%) were isolated. The IR spectrum of **2c** shows a C=N, CO_2Me, CO_2Et and NH stretching vibrations at 1620, 1720, 1745 and 3300 cm^{-1}, respectively. This observation was confirmed by ^{13}C NMR which indicates a qurtet at 14.1, qurtet at 52.4, triplet at 62.6, singlet at 156.2 and two singlets at 168.8 or 168.9 ppm characteristic for $CO_2CH_2\mathit{CH_3}$, CO_2CH_3, $CO_2\mathit{CH_2}CH_3$, C=N and ester carbonyl group of CO_2Me or CO_2Et respectively. Though *syn*-and *anti*-isomers were possible for **2**, only one isomer was produced, showing stereoselectivity in every case. However, stereochemistry of **2** is not clear. The dibenzoate **3c** was isolated as a diastereomeric mixture of *dl*- and *meso*-isomers. The isomer ratio was 1:1 as indicated from the ^{1}H NMR spectrum of the mixture. The isolation of **3c** would attributed to the stabilization of the radical **9** (Scheme 4) by the ethoxycarbonyl group and the anilino group through capto-dative resonance (push-pull resonance)[16-19]. In contrast the photoreactions of **1a** and **1b** radical **9** would be unstable because it is a primary in both cases and therefore, it is not formed and accordingly no dibenzoate derivative is formed from irradiation of **1a** and **1b**.

It is noteworthy to report that, in the photocyclization reactions of 2-alkoxybenzophenones (R' = Ph) Scheme 1, the preferential 1,5-cyclization of the 1, 5-biradical intermediate over 1,3-spirocyclization would attributed to the stability of the ketyl radical of the 1, 5-biradical intermediate by the second phenyl ring during cyclization to give benzofuran derivatives[3, 5, 16, 20]. In contrast, the hemiacetal radical of the 1, 5 biradical intermediate **5** formed by δ-hydrogen abstraction Scheme 4 would be unstable compared to the ketyl radical of benzophenone derivative. For effective 1, 5-cyclization to form indole derivatives **8**, rotation by 90^0 of *p*-orbital at hemiacetal radical is necessary. This rotation looses conjugation with the phenyl ring. Therefore, 1, 3-spirocyclization occurs preferentially to give imines **2a-c** instead of giving indoles **8**.

Finally, we discuss reaction pathways in the photoreactions of substiuted anthranilate ester **1a-c**. The mechanism of this type of reactions have been well studied[5, 11]. The mechanistic pathways of products formation are summarized in scheme 4. Irradiation of esters **1a-c** forms (n, π^*) excited triplet states **4** after intersystem crossing process (ISC). The carbonyl group abstracts δ-hydrogen to give 1, 5-biradical **5** which can undergo 1, 3-spirocyclization[1, 3, 5, 16] to the spiroaziridine **6**. The spiroaziridine intermediate undergoes ring opening to give rearranged 2-methoxycarbonylbenzylamines **7** and then oxidized with oxygen in solvent to give imines **2** as a final product. Production of **3c** is not so clear, however it would be produced *via* radical **9** which can do dimerization to afford the dibenzoate derivative **3c**.

In summary, photochemistry of anthranilate esters are useful to synthesize imine derivatives. The imine formed had only one stereoisomer in each case as indicated from their spectral measurements showing stereoselectivity. 1, 5-Cyclization, or 1, 3-spirocyclization depends on the stability of the 1, 5-biradical intermediate.

Scheme 4


1
1. hν
2. ISC
4
δ-Hydrogen abstraction
5
1, 5-cyclization
8
1, 3-cyclization
6
7
(O)
2
R1 = H, R2 = CO2Et
Hdrogen abstraction by excited molecule
9
dimerization
3c

Experimental:

The melting points are uncorrected. Column choromatography was performed on silica gel (Wakogel C-200). Ether refers to diethyl ether. Acetonitrile was dried by distillating over phosphorus pentoxide, then over potassium carbonate. Photoreactions were carried out with 400-W high-pressure mercury lamp (Riko UVL-400 HA) with Pyrex filter. The IR spectra were determined on a Hitachi Model 270-30 IR spectrometer. The ^{1}H and ^{13}C NMR spectra were determined at 200 MHz and 50 MHz on a Varian Gemini 200 FT NMR spectrometer, using tetramethylsilane as the internal standard.

Methylation of anthranilic acid.

A mixture of anthranilic acid (2.0 g, 14.6 mmoles), methyl iodide (4.2 g, 29.6 mmoles), tripotassium phosphate (6.2 g, 29.2 mmoles) and acetone (30 ml) was stirred at 60° for 120 minutes. After removal of insoluble materials by filteration the acetone was evaporated. The residue was chromatographed and eluted with benzene to give methyl N,N-dimethylanthranilate **1b** as a colorless oil (0.5 g, 19%); ir (neat): 1730 cm^{-1} (CO_2CH_3); ^{1}H NMR ($CDCl_3$): δ 2.86 [s, 6H, $N(CH_3)_2$], 3.90 (s, 3H, CO_2CH_3), 6.79-6.97 (m, 2H, Ar-H_2), 7.27-7.39 (m, 1H, Ar-H), 7.64-7.69 (m, 1H, Ar-H). Found: C, 66.90; H. 7.30; N, 7.79. $C_{10}H_{13}NO_2$ requires : C, 67.04; H, 7.26; N, 7.82.

The second product was methyl N-methylanthranilate **1a** isolated as a pale yellow oil (0.7 g, 29%)[15]; IR (neat): 3310 ($NHCH_3$) and 1735 cm^{-1} (CO_2CH_3); ^{1}H NMR ($CDCl_3$): δ 2.90 (d, J = 3Hz, 3H, $NHCH_3$), 3.85 (s, 3H, CO_2CH_3), 6.55-6.68 (m, 2H, Ar-H_2), 7.33-7.44 (m, 1H, Ar-H), 5.90 (broad s, exchangeable, 1H, *NH*CH_3), 7.87-7.92 (m, 1H, Ar-H).

The third product was methyl anthranilate **B** isolated as a colorless oil (0.6 g, 27%)[15]; IR (neat): 3300 (NH_2) and 1730 cm^{-1} (CO_2CH_3); ^{1}H NMR ($CDCl_3$): δ 3.86 (s, 3H, CO_2CH_3), 5.72 (broad s, exchangeable, 2H, NH_2), 6.60-6.68 (m, 2H, Ar-H_2), 7.22-7.30 (m, 1H, Ar-H), 7.80-7.91 (m, 1H, Ar-H).

Reaction of ethyl bromoacetate with methyl anthranilate A.

A mixture of methyl anthranilate (3.1 g, 20.5 mmoles), ethyl bromoacetate (7.5 gm, 44.9 mmoles), potassium carbonate (5.67 gm, 40.8 mmoles) and dimethyl sulfoxide (30 ml) was stirred at 60° for 180 minutes. After removal of insoluble materials by filteration the filtrate was poured into water and extracted with ether. The extract was washed, dried and evaporated. The residue was chromatographed and eluted with benzene (95)-ether (5) to give Ethyl N-(2-methoxycarbonylphenyl)glyine ester **1c** as a colorless crystal (3.2 g, 66%) from benzene-hexane, mp 46-47° ; IR (KBr): 3360 (NH) and 1740 cm^{-1} (CO_2CH_3 and $CO_2CH_2CH_3$); ^{1}H NMR ($CDCl_3$): δ 1.29 (t, J = 6 Hz, 3H, $CO_2CH_2CH_3$), 3.87 (s, 3H, CO_2CH_3), 3.98 (d, J = 3 Hz, 2H, $NHCH_2$), 4.25 (q, J = 6 Hz, 2H, $CO_2CH_2CH_3$), 6.48-6.54 (m, 1H, Ar-H), 6.55-6.68 (m, 1H, Ar-H), 7.30-7.41(m, 1H, Ar-H), 7.87-7.94 (m, 1H, Ar-H), 8.19 (broad s, exchangeable, 1H, *NH*CH_2); ^{13}C NMR ($CDCl_3$): δ 14.1 (q), 44.9(q), 51.5(t), 61.3 (t), 110.9 (s), 111.1(d), 115.5 (d), 131.7 (d), 134.5 (d), 149.8 (s), 168.7 (s), 170.3 (s). Found: C, 60.75; H. 6.36; N, 5.94. $C_{12}H_{15}NO_4$ requires : C, 60.76; H, 6.33; N, 5.91.

General Procedure for Photoreactions of Esters 1a-c.

In acetonitrile solvent (500 ml), 2.00 mmoles of the starting materials **1a-c**, were dissolved. The solution was deoxygenated by bubbling nitrogen gas for 1 hour and then irradiated under monitoring by high performance liquid chromatography (hplc) or TLC. The irradiation was stopped at the exact time (see table 1). After irradiation the solvent was evaporated under reduced pressure below 40°. The residue was chromatographed and eluted with benzene-ether to give different products.

***syn-* or *anti*-N-2-Methoxycarbonylbenzylideneamine 2a.**

Compound **2a** was obtained as colorless oil; IR (neat): 3320 (NH), 1720 (CO_2CH_3) and 1610 cm^{-1} (C=N) ; ^1H NMR ($CDCl_3$): δ 3.94 (s, 3H, CO_2CH_3), 7.13 (dd, J = 4 and 4 Hz, 1H, Ar-H), 7.52 (dd, J = 4 and 4 Hz, 1H, Ar-H), 8.05 (d, J = 4 Hz, 1H, Ar-H), 8.52 (s, 1H, CH=N), 8.71 (d, J = 4 Hz, 1H, Ar-H), 10.90 (broad s, exchangeable, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 52.3 (q), 115.5 (s), 121.1 (d), 123.0 (d), 130.8 (d), 134.6 (d), 140.3 (s), 159.5 (d), 168.4 (s). Found: C, 66.28; H. 5.53; N, 8.60. $C_9H_9NO_2$ requires: C, 66.26; H, 5.52; N, 8.59.

***syn-* or *anti*-N-(2-Methoxycarbonyl-benzylidene)methylamine 2b.**

Compound **2b** was obtained as colorless oil; IR (neat): 1720 (CO_2CH_3) and 1620 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 3.29 (s, 3H, N-CH_3), 3.96 (s, 3H, CO_2CH_3), 7.14 (dd, J = 4 and 4 Hz, 1H, Ar-H), 7.54 (dd, J = 4 and 4 Hz, 1H, Ar-H), 8.06 (d, J = 4 Hz, 1H, Ar-H), 8.54 (s, 1H, CH=N), 8.69 (d, J = 4 Hz, 1H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 45.5 (q), 52.4 (q), 115.3 (s), 121.1 (d), 123.1 (d), 131.1 (d), 134.5 (d), 140.6 (s), 159.5 (d), 168.9 (s). Found: C, 67.83; H. 6.25; N, 7.90. $C_{10}H_{11}NO_2$ requires : C, 67.80; H, 6.21; N, 7.91.

***syn-* or *anti*-Ethyl 2-(2-Methoxycarbonylphenyl)-2-iminoethanoate 2c.**

Compound **2c** was obtained as colorless oil; IR (neat) 3330 (NH), 1720 (CO_2CH_3 or $CO_2CH_2CH_3$), 1745 ($CO_2CH_2CH_3$ or CO_2CH_3) and 1620 cm^{-1} (C=N) ; ^1H NMR ($CDCl_3$): δ 1.44 (t, J = 6 Hz, 3H, $CO_2CH_2CH_3$), 3.89 (s, 3H, CO_2CH_3), 4.45 (q, J = 6 Hz, 2H, $CO_2CH_2CH_3$) 7.22 (dd, J = 4 and 4 Hz, 1H, Ar-H), 7.40 (dd, J = 4 and 4 Hz, 1H, Ar-H), 8.08 (d, J = 4 Hz, 1H, Ar-H), 8.74 (d, J = 4 Hz, 1H, Ar-H), 12.56 (broad s, exchangeable, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 14.1 (q), 52.4 (q), 62.6 (t), 111.1 (s), 120.4 (d), 124.0 (d), 131.1 (d), 134.6 (d), 139.8 (s), 156.2 (s), 168.8 (s), 168.9 (s). Found: C, 61.31; H. 5.52; N, 5.98. $C_{12}H_{13}NO_4$ requires: C, 61.28; H, 5.53; N, 5.96.

***dl-* and *meso*-Dimethyl 2, 2'-[1, 2-Diethoxycarbonylethylene-diamino]dibenzoate 3c.**

These diastereoisomers of **3c** were obtained as a 1:1 mixture (oil). It was difficult to isolate each isomer in a pure state.

The first isomer had IR (neat): 3350 (NH), 1745 ($CO_2CH_2CH_3$ and CO_2CH_3) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.29 (t, J = 6 Hz, 3H, $CO_2CH_2CH_3$), 3.25 (d, J = 3 Hz, 1H, NH*CH*), 3.88 (s, 3H, CO_2CH_3), 4.12-4.36 (m, 2H, $CO_2CH_2CH_3$),

6.62-6.78 (m, 1H, Ar-H), 7.26-7.41 (m, 1H, Ar-H). 7.88-7.99 (m, 1H, Ar-H), 8.42 (d, J = 5 Hz, 1H, Ar-H), 11.3 (broad s, exchangeable, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 14.0 (q), 51.7 (q), 61.9 (t), 71.5 (d), 111.6 (s), 111.8 (d), 116.2 (d), 131.9 (d), 134.3 (d), 149.2 (s), 168.5 (s), 171.7 (s).

The second isomer had IR (neat): 3350 (NH), 1745 ($CO_2CH_2CH_3$ and CO_2CH_3) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.34 (t, J = 6 Hz, 3H, $CO_2CH_2CH_3$), 3.41 (d, J = 3 Hz, 1H, NHCH), 3.89 (s, 3H, CO_2CH_3), 4.61-4.82 (m, 2H, $CO_2CH_2CH_3$), 6.62-6.78 (m, 1H, Ar-H), 7.26-7.41 (m, 1H, Ar-H). 7.88-7.99 (m, 1H, Ar-H), 8.58 (d, J = 5 Hz, 1H, Ar-H), 11.6 (broad s, exchangeable, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 14.1 (q), 51.7 (q), 62.4 (t), 71.6 (d), 112.1 (d), 112.2 (s), 116.3 (d), 132.0 (d), 134.5 (d), 149.6 (s), 168.6 (s), 171.9 (s).

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