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Synthesis and photoreactivity of some 5-alkylidene- and 5-alkylidenamine-2,5-dihydroisoxazoles

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Abstract

5-Alkylidene-2,5-dihydroisoxazoles and 5-alkylidenamine-2,5-dihydroisoxazoles were easily prepared from the corresponding 5-chloro-2-methylisoxazolium triflate and an enolizable compound or alkylamine. Their photochemical reactivity leads to photoisomers that in some cases constitute new heterocycles systems. The photorearrangement involves either triplet or singlet state depending on substituents and experimental conditions.

Keywords: Isoxazole; Photochemistry; Singlet and triplet state; Triplet sensitizers

The isomerization of heterocycles is an important area of organic photochemistry[1] and, amongst the heterocycles, the isoxazolic system is one of the most widely studied.[2] These photoisomerizations involve different intermediates,[3] which show a number of interesting reactions. The 2*H*-isoxazol-5-ylidene system is a heterocyclic ring analogous to isoxazole but was scarcely considered. The few studies reported in the literature on these products go back to the early 70s[4] and more recently a single example of the reactivity of 2,5-dihydroisoxazolonic systems[5] was reported.

In recent years, we found a convenient procedure for the synthesis of a series of 5-alkylidene-2,5-dihydroisoxazoles[6] and we studied their photochemical behaviour. These compounds photoisomerized to β-lactam and/or γ-dihydrolactone systems depending on the substituents on the exocyclic double bond. A cyclopropanone intermediate accounted for all products so far obtained (Scheme 1).

Recently we synthetized compound **1a**,[7] which unexpectedly showed a different photoreactivity in respect to that already known.[6] Irradiation under the usual experimental conditions[8] gave only the spiro-photoisomer **2a**[8] (Scheme 2), hardly justifiable on the basis of a cyclopropanone intermediate.

The structure of **2a** was determined by X-ray diffractometric analysis (Fig. 1).

This result prompted us to carry out a wider survey on the photoisomerization of such systems, and we planned to extend our studies towards 2*H*-isoxazol-5-yliden systems bearing an exocyclic C=N double bond.

First of all, we devised a general method for the synthesis for the 2*H*-isoxazol-5-ylidenamine derivatives. Treatment of the corresponding 5-chloro-2-methylisoxazolium triflate[6a] with amines led to substitution products which, in turn, were deprotonated in the presence of alkoxide yielding the (2*H*-isoxazol-5-ylidene)-alkylamines **1b**–**d**[9] (Scheme 3).

Irradiation of **1b**–**d**[10] in CH_3CN resulted in the formation of the products reported in Scheme 4.

Irradiation of a solution of **1b** in CH_3CN yielded both the imidazolonic and pyrazolonic derivatives **2b**[11] and **3b**,[12] whereas under the same experimental conditions **1c** and **1d** yielded only the corresponding imidazolones **2c**[11] and **2d**.

Following the irradiation of **1b**[10a] in CD_3CN by ^1H NMR, we noticed that the ratio **2b/3b** was changing in

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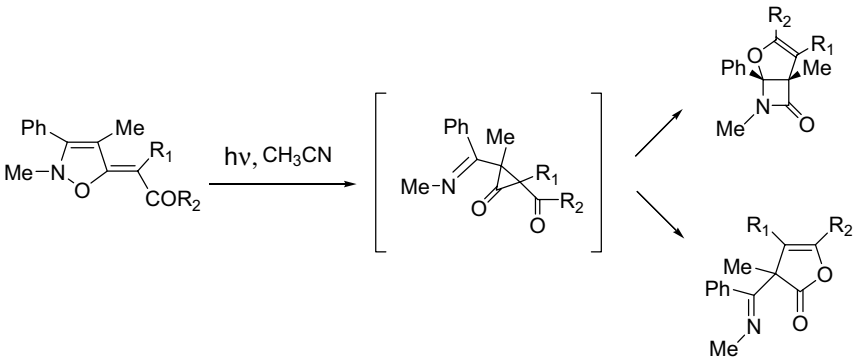
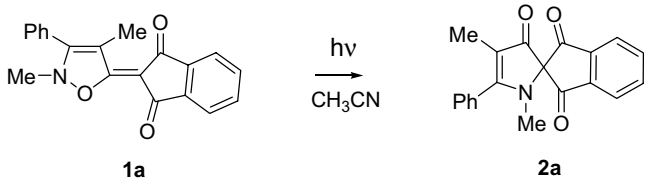


Scheme 1.



Scheme 2.

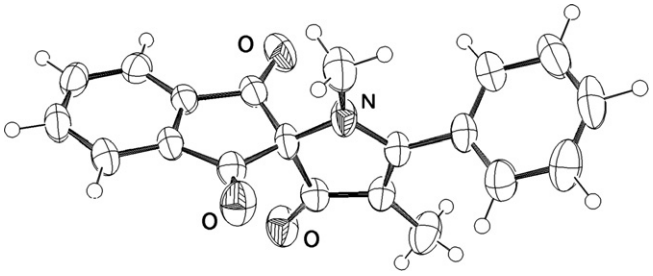
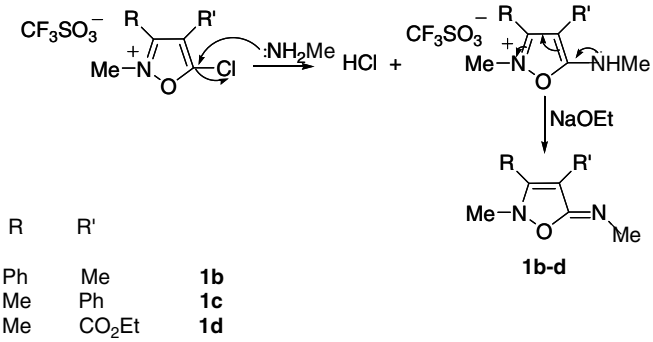


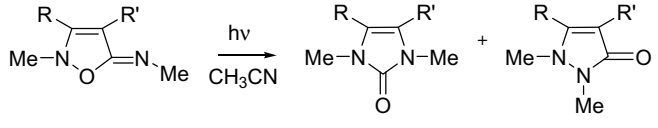
Fig. 1. ORTEP drawing of compound **2a** with 20% probability thermal ellipsoids (CCDC 632412).



R	R'	
Ph	Me	**1b**
Me	Ph	**1c**
Me	CO_2Et	**1d**

Scheme 3.

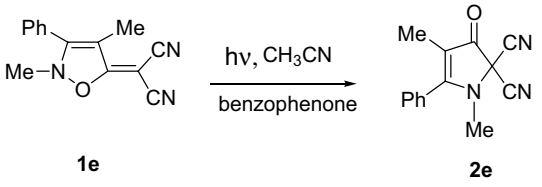
time, in particular the amount of **3b** increases after a long induction period, starting to rise when the amount of **2b** is near its maximum and reaching roughly a 1/1 ratio at the end of the reaction. The hypothesis that **3b** could derive from **2b** has been discarded: in fact the irradiation of the imidazolonic derivative does not lead to **3b**, but only to an unidentified mixture of degradation products.



R	R'	
Ph	Me	**1b**
Me	Ph	**1c**
Me	CO_2Et	**1d**

Scheme 4.

Experiments of sensitization clarified the multiplicity of the states involved and suggested an explanation for the time dependent ratio of the concentrations of **2b/3b**. Irradiation of **1b**[10b] in the presence of acetophenone, a typical triplet state sensitizer, gave only pyrazolone **3b**, whereas



Scheme 5.

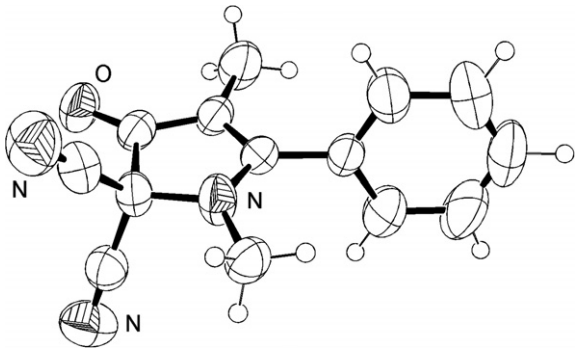
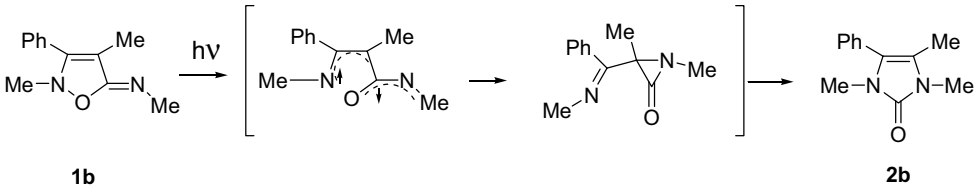
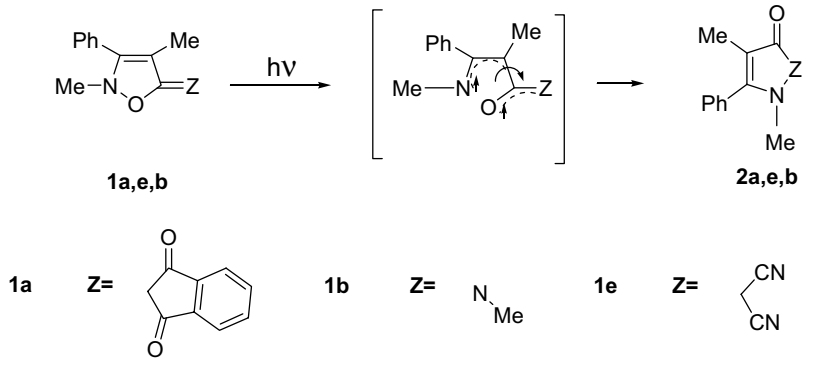


Fig. 2. ORTEP drawing of compound **2e** with 20% probability thermal ellipsoids (CCDC 632412).



Scheme 6.



Scheme 7.

irradiation in the presence of piperylene,[10c] a typical triplet quencher, gave only imidazolone **2b**. The induction period is so explained supposing that **2b**, initially formed via singlet state, behaves as triplet sensitizer for **3b**. Experimentally an increase in the rate of formation of **3b** was observed when the irradiation of **1b** was performed in the presence of **2b** since the beginning. But also the presence of a pyrazolonic system itself sensitizes the reaction towards the formation of **3b**. In fact, irradiating **1b** in the presence of 1,2-hexadeuteromethyl-4-methyl-5-phenyl-1,2-dihydro-pyrazol-3-one[13] and monitoring the yield of non-deuterated **3b** by ^{1}H NMR, we observed the lack of the induction period and the yield of **3b** greater than **2b** since the beginning of irradiation.

Similar sensitization experiments are difficult to realize on the alkylidene isoxazole system, owing to the overlap of the absorption bands. However, a strong indication that an analogous mechanism is operating was obtained by irradiating the dinitrile derivative **1e**.[7] Irradiation of **1e** in CH_3CN did not yield any characterizable product, but in the presence of benzophenone[14] as sensitizer, pyrrolidone **2e**[14] was obtained in good yield (Scheme 5).

The structure of **2e** was determined by X-ray diffractometric analysis (Fig. 2).

The data obtained allowed us to rationalize the pathways of photoisomerization, both for the 5-alkylidene and 5-alkylidenamine-2,5-dihydroisoxazole as summarized in Schemes 6 (singlet pathway) and 7 (triplet pathway).

In the case of alkyliden amine derivatives the aziridinone intermediate arises from a singlet state and rearranges to the imidazolonic system (Scheme 6) in analogy to the corresponding pathway reported in Scheme 1 for alkylidene-2,5-dihydroisoxazole.

When these rearrangements are not possible, as in the case of substrate **1e**, no opening products were isolated.

On the other hand the triplet state, populated by either intersystem crossing (cases **1a**,**b**) or sensitization (**1b**,**e**), evolves to new products formally derived from rotation of the C4–C5 bond and ring closure by N–N or C–N bond formation (Scheme 7).

In summary we have described a simple and general method for the synthesis of a series of 2,5-dihydroisoxazoles bearing a C=C or C=N exocyclic double bond in position 5 and we have studied their photochemical reactivity. From the mechanistic point of view, two different pathways arising from states of different multiplicity are possible. State-switching is attainable by changing the nature of the substituents on the exocyclic double bond and/or by using quenchers or sensitizers. In this way it is possible to direct the reactions to the required products obtaining cleanly new heterocycles from easily accessible materials.

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7. *Synthesis of products* **1a**,**e**: To a stirred solution of compound with easy deprotonable CH_2 [malononitrile (3 mmol) or 1,3-indandione (3 mmol)] in anhydrous benzene (15 mL) were sequentially added

NaH 60% in oil (3 mmol) and dry Et_3N (3 mmol). To this suspension was then slowly added 5-chloro-2,4-dimethyl-3-phenylisoxazol-2-ium trifluoromethanesulfonate (3 mmol) and the resulting yellow solution stirred for 1 h. After this time the reaction mixture was concentrated in vacuo and the residue treated with water (20 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The organic layer was dried over Na_2SO_4, the solvent evaporated and the resulting oil purified by column chromatography (eluent CH_2Cl_2/CH_3OH 98:2 for compound **1e** and ethyl acetate/CH_3OH 95:5 for compound **1a**).

Experimental data: melting points were measured with a Kofler apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded for solution in $CDCl_3$, save otherwise stated, with a Bruker AC200 instrument operating at 200.13 MHz for ^1H and at 50.33 MHz for ^{13}C. ESI-MS spectra were recorded with a LCQ-DECA Thermo Finnigan instrument, and EI-MS spectra were obtained with a VG70 250S instrument. TLC was performed on precoated 4 × 6.7 cm silica gel 60 F254 plates silica gel (Aldrich) with detection by UV light. Column chromatography was carried out on Silica gel (E. Merck, 0.040–0.063 mm). Irradiation was performed with a Rayonet apparatus (MLU18) operating at 365 nm, with a 900 W irradiator, f/3.4 monochromator (Applied Photophysics) apparatus or with a low pressure mercury lamp (253.7 nm). All irradiations were carried out in CH_3CN in the presence of activated molecular sieves (0.4 nm, 100–150 mg). At the end of the irradiations the molecular sieves were decanted and washed with a further CH_3CN (10 mL).

2-(2,4-Dimethyl-3-phenylisoxazol-5(2H)-ylidene)-2H-indene-1,3-dione (**1a**): yellow-orange solid (65% yield), mp 258–260 °C (ethyl acetate); ^1H NMR δ: 2.26 (s, 3H, 4′-CH_3), 3.79 (s, 3H, N–CH_3), 7.34–7.56 (m, 9H, Ph); ^{13}C NMR δ: 9.52 (4′-CH_3), 37.97 (N–CH_3), 96.87 (C_2), 108.18 ($C_{4'}$), 120.03, 124.18, 128.75, 129.41, 131.60, 131.66, 139.78 (Ph), 157.71 ($C_{3'}$), 170.79 ($C_{5'}$), 188.86 (1,3-CO); ESI-MS, *m/z*: 318 ($M-H^+$). Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.70; H, 4.76; N, 4.41. Found: C, 75.67; H, 4.78; N, 4.38.

2-(2,4-Dimethyl-3-phenylisoxazol-5(2H)-ylidene)malononitrile (**1e**): yellow solid (60% yield), mp 205–207 °C; ^1H NMR δ: 2.15 (s, 3H, 4-CH_3), 3.49 (s, 3H, N–CH_3), 7.38–7.60 (m, 5H, Ph); ^{13}C NMR δ: 8.01 (4-CH_3), 39.40 (N–CH_3), 40.72 (C_2), 104.37 (C_4), 115.52 (CN), 124.47, 128.69, 129.59, 131.86 (Ph), 159.88 (C_3), 176.11 (C_5); ESI-MS, *m/z*: 497 ($2M-Na^+$). Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 71.02; H, 4.63; N, 17.79.

8. *1′,4′-Dimethyl-5′-phenylspiro[indene-2,2′-pyrrole]-1,3,3′(1′H)-trione* (**2a**): A solution of **1a** (1 mmol) in anhydrous CH_3CN (40 mL) was irradiated for 24 h in a pyrex tube. After this time the solvent was removed in vacuo. The crude reaction obtained was purified by column chromatography (eluent ethyl acetate/petroleum ether 1:1) to give starting material (30%) and pure compound **2a**, as a yellow solid (40% yield), mp 135–138; ^1H NMR δ: 1.57 (s, 3H, 4′-CH_3); 2.81 (s, 3H, N–CH_3), 7.49–7.51 (m, 5H, Ph), 7.89–7.85 (m, 2H, H*m*), 8.08–8.03 (m, 2H, H*o*); ^{13}C NMR δ: 7.52 (4′-CH_3), 32.32 (N–CH_3), 87.25 (C_2), 105.74 ($C_{4'}$), 124.38, 128.34, 128.76, 129.45, 130.32, 136.05, 143.26 (Ph), 178.47 ($C_{5'}$), 189.87 (3′-CO), 190.18 (1,3-CO); ESI-MS, *m/z*: 340 ($M-Na^+$). Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.70; H, 4.76; N, 4.41. Found: C, 75.72; H, 4.72; N, 4.39.

9. *Synthesis of products* **1b–d**: to a solution of CH_3NH_2 (2 mmol) in anhydrous THF was added 2 mmol of the appropriate 5-chloro-2-methylisoxazolium triflate obtaining a white precipitate. An excess of sodium ethoxide was added. After evaporation of the solvent the residual pale yellow solid was treated with chloroform. After filtration of the white solid, the solvent was evaporated and the final product purified by sublimation.

(2,4-Dimethyl-3-phenyl-2*H*-isoxazol-5-ylidene)-methylamine (**1b**): white solid (75% yield), mp 73–76 °C; ^1H NMR δ: 1.91 (s, 3H, 4-CH_3), 2.92, 3.10 (s, 3H, C=NCH_3/2-NCH_3), 7.45 (m, 5H, Ph); ^{13}C NMR δ: 6.74 (4-CH_3), 30.18, 40.70 (C=NCH_3/2-NCH_3), 99.44 (C_4), 125.05, 128.68, 129.64, 131.90 (Ph), 162.68, 168.84 (C_3/C_5); EI-MS, *m/z*: 202 (M^+), 185, 173. Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.00; H, 7.00; N, 13.91. (2,3-Dimethyl-4-phenyl-2*H*-isoxazol-5-ylidene)-methylamine (**1c**): gummy solid (60% yield); ^1H NMR δ: 2.10 (s, 3H, 3-CH_3), 3.11, 3.17 (s, 3H, C=NCH_3/NCH_3), 7.45 (m, 5H, Ph); ^{13}C NMR δ: 11.01 (3-CH_3), 33.61, 40.40 (C=NCH_3/NCH_3), 109.30 (C_3), 127.30, 128.28, 129.78, 131.90 (Ph), 155.89, 161.00 (C_4/C_5); EI-MS, *m/z*: 202 (M^+), 185, 173. Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.41; H, 6.95; N, 13.88.

(2,3-Dimethyl-4-carbethoxy-2*H*-isoxazol-5-ylidene)-methylamine (**1d**): oil (65% yield); ^1H NMR δ: 1.34 (t, 3H, $J = 7.2$ Hz, CH_2CH_3), 2.42 (s, 3H, 3-CH_3), 3.05, 3.52 (s, 3H, NCH_3/C=NCH_3), 4.30 (q, 2H, $J = 7.2$ Hz, CH_2CH_3); ^{13}C NMR δ: 12.23 (CH_2CH_3), 14.26 (3-CH_3), 32.73, 36.76 (C=NCH_3/NCH_3), 60.58 (CH_2CH_3), 93.07 (C_4), 159.30, 160.93, 162.76 (C=N/C=O/C_3); EI-MS, *m/z*: 198 (M^+), 184, 170, 153. Anal. Calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.30; H, 7.09; N, 14.18.

10. *Procedures for the irradiation of* **1b–d**: (a) a solution of **1b–d** (2 mmol) in anhydrous CH_3CN (10 mL) was irradiated for 3 h in a quartz tube at 254 nm. After this time the solvent was removed in vacuo. The crude reaction mixture obtained was purified by column chromatography ($CHCl_3/CH_3OH$ 98:2) to give pure compounds **2b–d** and **3b**. 1,3,4-trimethyl-5-carbethoxy-1,3-dihydro-imidazol-2-one (**2d**): white solid (60% yield), mp 58–62 °C; ^1H NMR δ: 1.34 (t, 3H, $J = 7.3$ Hz, CH_2CH_3), 2.38 (s, 3H, 4-CH_3), 3.24, 3.47 (s, 3H, 3-NCH_3/1-NCH_3), 7.20-7.50 (m, 5H, Ph); ^{13}C NMR δ: 10.50 (CH_2CH_3), 13.69 (4-CH_3), 26.81, 29.29 (3-NCH_3/1-NCH_3), 54.47 (CH_2CH_3), 109.71 (C_4), 130.45 (C_5), 152.31 (C_2), 159.90 (CO); EI-MS, *m/z*: 198 (M^+), 184, 170, 153. Anal. Calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.60; H, 7.14; N, 14.17.

(b) A solution of **1b** (0.1 mmol) and acetophenone (10 mmol) in anhydrous CH_3CN (3 mL) (sol. a) and at the same time a solution of **1b** (0.1 mmol) in anhydrous CH_3CN (3 mL) (sol. b) were irradiated for 10 h in a pyrex tube in a merry go round system, monochromatic light (365 nm). After this time the solvent was removed in vacuo and both spectroscopic and chromatographic analyses indicated that in (sol. a) **3b** was present, while in (sol. b) only **1b** was present.

(c) A solution of **1b** (0.1 mmol) and piperylene (10 mmol) in anhydrous CH_3CN (3 mL) (sol. a) and at the same time a solution of **1b** (0.1 mmol) in anhydrous CH_3CN (3 mL) (sol. b) were irradiated for 12 h in a quartz tube in a merry go round system, monochromatic light (254 nm). After this time the solvent was removed in vacuo and both spectroscopic and chromatographic analyses indicated that in (sol. a) **2b** was present, while in (sol. b) both **2b** and **3b** were present.

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13. *Synthesis 1,2-esadeuteromethyl-4-methyl-5-phenyl-1,2-dihydro-pyrazol-3-one*: Ethyl benzoyl propionate (9.0 mmol) and trideuteromethyl hydrazine (4.5 mmol) were heated to 180 °C for 1 h. After evaporation a small excess of sodium methoxide (10.0 mmol of Na in 5 mL of CH_3OH) and subsequently CD_3I (11 mmol) were added, and refluxed for 1 h. The solvent was evaporated and the resulting mixture purified by column chromatography (eluent CH_2Cl_2/CH_3OH 95:5) to give 1,2-esadeuteromethyl-4-methyl-5-phenyl-1,2-dihydro-pyrazol-3-one, white solid (50% yield), mp 136–138 °C; ^1H NMR (CD_3CN) δ: 1.81 (s, 3H, 4-CH_3), 7.20–7.38 (m, 5H, Ph); ^{13}C NMR (CD_3CN) δ: 7.90 (4-CH_3), 107.91 (C_4), 128.67, 129.12, 129.56, 129.78 (Ph), 153.85 (C_3), 165.99 (C_5); EI-MS, *m/z*: 208 (M^+), 193, 179.

14. *1,4-Dimethyl-3-oxo-5-phenyl-1H-pyrrole-2,2(3H)-dicarbonitrile* (**2e**): a solution of **1e** (1 mmol) and benzophenone (10 mmol) in anhydrous CH_3CN (40 mL) was irradiated for 8 h in a pyrex tube at 365 nm. After this time the solvent was removed in vacuo. The crude reaction mixture obtained was purified by column chromatography (eluent ethyl ether/petroleum ether 1:2) to give pure compound **2e**, as a red solid (40% yield), mp 105–107 °C; ^1H NMR δ: 1.67 (s, 3H, 4-CH_3), 3.02 (s, 3H, N–CH_3), 7.31–7.60 (m, 5H, Ph); ^{13}C NMR δ: 7.84 (4-CH_3), 15.20 (N–CH_3), 57.06 (C_2), 107.17 (C_4), 109.51 (CN), 127.86, 129.32, 129.99, 131.66 (Ph), 177.58 (C_5), 182.32 (CO); ESI-MS, *m/z*: 497 ($2M-Na^+$). Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 71.02; H, 4.71; N, 17.80.