Single electron transfer photoinduced oxidation of piperidine and pyrrolidine derivatives to the corresponding lactams

Guillaume Cocquet,[a] Clotilde Ferroud,*[a] Patrice Simon[b] and Pierre-Louis Taberna[b]

[a] *Laboratoire de Chimie Organique associé au CNRS, Conservatoire National des Arts et Métiers, 292, rue Saint Martin, F-75141 Paris Cedex 03, France*
[b] *Laboratoire d'Electrochimie, Conservatoire National des Arts et Métiers, 292, rue Saint Martin, F-75141 Paris Cedex 03, France*

Received (in Cambridge, UK) 7th February 2000, Accepted 20th March 2000
Published on the Web 9th May 2000

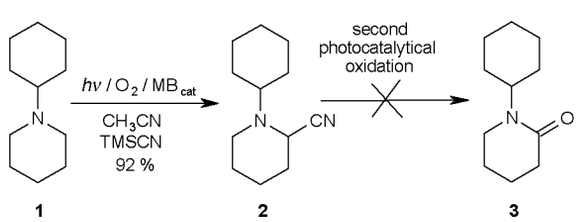
Irradiation by visible light of various *N*-arylaminopiperidines or *N*-arylaminopyrrolidines in presence of a catalytic amount of photosensitizer led with good yields to the corresponding *N*-arylaminolactams under mild conditions. This reaction proceeds by two consecutive photooxidations, the first in presence of trimethylsilyl cyanide and the second one in presence of water. Voltammetric investigations demonstrated clearly that hydrazines are more readily oxidised than tertiary amines, and as a consequence it is possible to obtain by photooxidation a wider range of oxidised compounds.

Introduction

Photooxidation by single electron transfer (SET) using visible light is often a mild and efficient alternative to the use of classical oxidising agents. For example photocyanation by SET of tertiary amines has allowed us to obtain α-aminonitriles[1–4] with good yields, whereas the typical chemical method (the Polonovski–Potier reaction[5,6]) requires an oxidation to the *N*-oxide and its transformation to an iminium ion intermediate with trifluoroacetic anhydride, followed by trapping with cyanide anions. Another alternative method was proposed by Hurvois and co-workers: anodic cyanation of *N*-substituted 1-benzazepines,[7] *N*-substituted tetrahydroquinolines and *N*-phenylpiperidines.[8] We are now interested in oxidising piperidine or pyrrolidine compounds to lactams under our photochemical conditions, in order to achieve an alternative to the conventional approaches (MnO_2, CrO_3–pyridine, *etc.*).

Results

Some examples of such photooxidations have been reported.[9,10] However, the range of examples is somewhat limited and yields are at best only modest. For example, irradiation with visible light ($\lambda > 630$ nm) of the 1-cyclohexylpiperidine **1** (Scheme 1) under oxygen with a catalytic amount



Scheme 1

of methylene blue (MB) as photosensitiser leads only to the degradation of the substrate. The presence of trimethylsilyl cyanide (TMSCN) as the cyanide ion source is necessary for the photooxidation of the piperidine **1**, and the cyano product **2** is obtained with a good yield (92%).

We did not succeed in converting the α-aminonitrile **2** into the lactam **3** with a catalytic amount of photosensitiser. The absence of electron-donating ability of α-aminonitrile **2** is estimated from the oxidation potential measured by means of cyclic voltammetry. The voltammograms of the tertiary amine **1** and the α-aminonitrile **2** (measured in acetonitrile at a 50 mV s^{-1} scan rate, with tetraethylammonium tetrafluoroborate (0.5 M) as a supporting electrolyte) each present one irreversible peak, respectively recorded at the peak potential $E_{p_1} = 1.02$ V and at $E_{p_2} = 1.47$ V (Fig. 1a and 1b). This voltammetric study confirms an increase in the oxidation potential (+0.45 V) as a result of the presence of a cyano group in the α position. Thus, the oxidising species, singlet oxygen or excited MB, are insufficiently oxidising to realise the oxidation of the α-aminonitrile **2** to the lactam **3**.

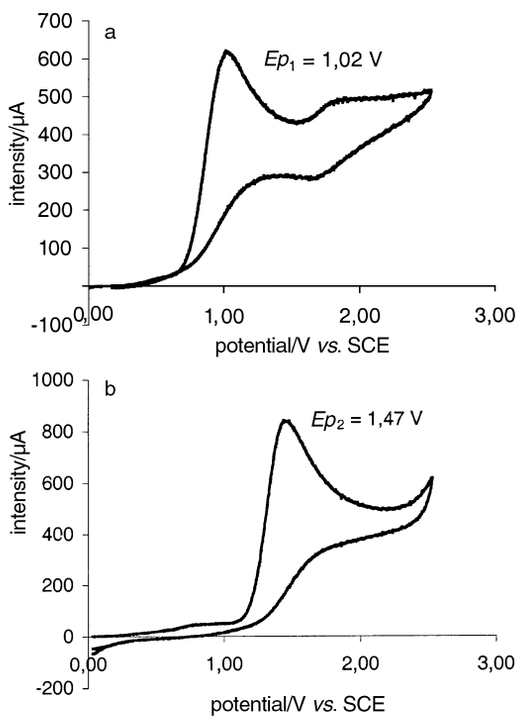


Fig. 1 Voltammetric investigations of compounds **1** (a) and **2** (b) in $CH_3CN + NEt_4BF_4$ (0.5 M), scan rate = 50 mV s^{-1}.

DOI: 10.1039/b001036g

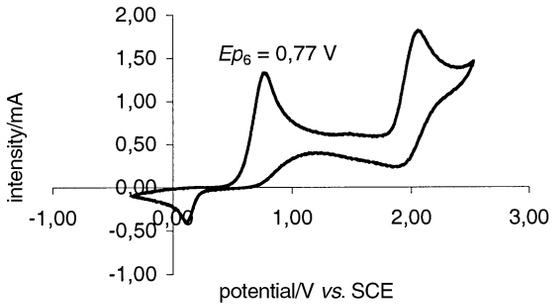
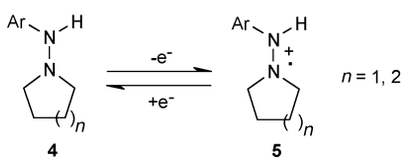


Fig. 2 Voltammetric investigations of compound **6** in CH_3CN + NEt_4BF_4 (0.5 M), scan rate = 50 mV s^{-1}.

Owing to the rather high oxidation potentials of the α-aminonitriles, we decided to investigate the photooxidation of other *N*-substituted piperidine and pyrrolidine derivatives which present lower oxidation potentials. We therefore chose *N*-arylamino-1-piperidines and *N*-arylaminopyrrolidines **4** because the formal charge of the hydrazinium radical cation **5** is distributed over the two nitrogen atoms (Scheme 2). Such delocalis-

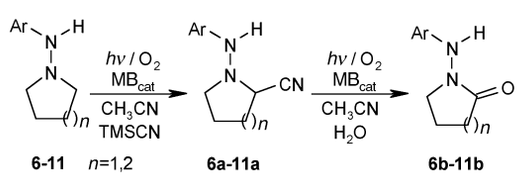


Scheme 2

ation explains their lower oxidation potential than in the case of tertiary amines.[11,12]

Indeed, if we compare the voltammogram of the amine **1** (Fig. 1a) with that of the 1-[(4-nitrophenyl)amino]piperidine **6** (Fig. 2), there is a difference between the oxidation potentials ($E_{p_1} - E_{p_6}$) of 0.25 V.

The general method used to oxidise the *N*-arylamino-piperidines or -pyrrolidines **6**–**11** is shown in Scheme 3. The first



Scheme 3

oxidation is performed using the methodology that we recently described:[13] the irradiation ($\lambda > 630$ nm) of the hydrazine derivatives **6**–**11** in the presence of bubbling oxygen, TMSCN and a catalytic amount of MB gives α-hydrazinonitriles **6a**–**11a** in good yields (59–100%). A second oxidation of these products with water as nucleophile instead of cyanide ion gives lactams **6b**–**11b** in moderate to good yields (45–95%). Some representative results are shown in Table 1.

This methodology allows us to synthesize a wide range of substituted lactams. For example, the alkylation of the cyano product **8a** with Grignard reagents yields the 2-substituted piperidine derivatives **12**–**15** (Scheme 4 and Table 2). Their photocyanation yields a mixture of the regioisomers which are not separated. The second photooxidation with water as nucleophile yields the lactams **12a**–**15a** in moderate yields (34–56%). All the results of the reaction sequence are shown in Table 2.

Discussion

These results clearly indicate that the α-hydrazinonitriles **6a**–**11a** obtained by photocyanation are readily oxidised to the corresponding hydrazides in good yields as shown in Table 1.

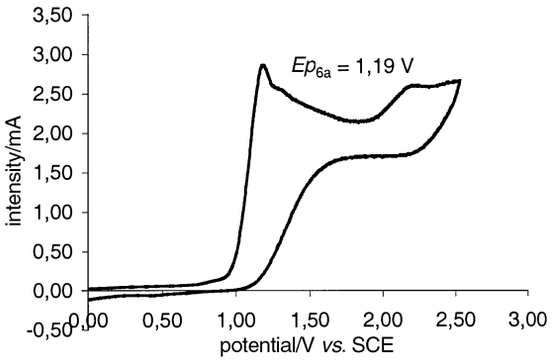
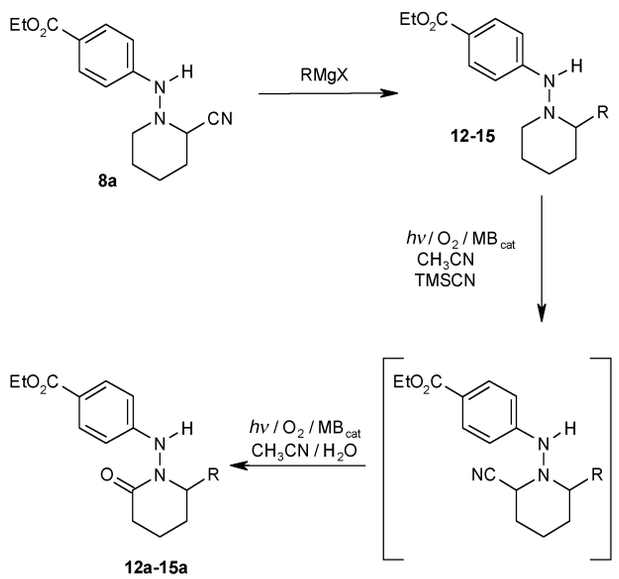


Fig. 3 Voltammetric investigations of compound **6a** in CH_3CN + NEt_4BF_4 (0.5 M), scan rate = 50 mV s^{-1}.



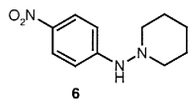
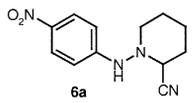
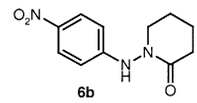
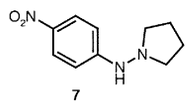
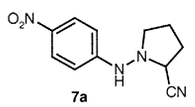
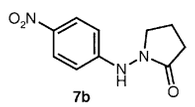
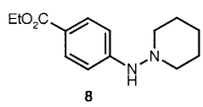
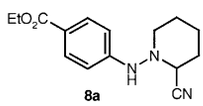
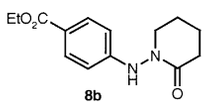
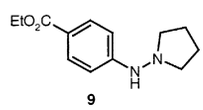
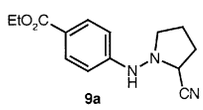
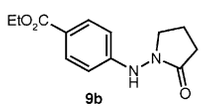
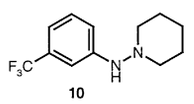
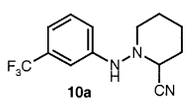
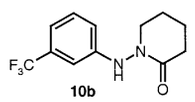
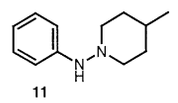
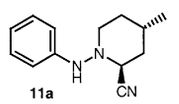
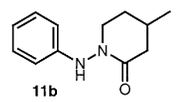
Scheme 4

The introduction of an alkyl substituent on the carbon atom next to the nitrogen atom decreases the regioselectivity of the cyanation. Thus, by-products corresponding to 2-cyano-2-alkylpiperidine derivatives are observed. A second photooxidation of these compounds in water affords the C–N bond cleavage product as previously described.[14]

Direct evidence for the oxidation step of α-aminonitriles compared to α-hydrazinonitriles is obtained by means of cyclic voltammetry (Fig. 3). Figs. 1(b) and 3 show cyclic voltammograms in acetonitrile at a 50 mV s^{-1} scan rate, of 2-cyano-*N*-cyclohexylpiperidine **2** and 1-[(4-nitrophenyl)-amino]piperidine-2-carbonitrile **6a** respectively, with tetraethylammonium tetrafluoroborate (0.5 M) as a supporting electrolyte. These electrochemical results demonstrate the greater ease of oxidation of the α-hydrazinonitriles than the corresponding α-aminonitriles (*i.e.* 1.19 V compared to 1.47 V). They are consistent with the fact that this process involves a catalytic amount of MB under bubbling oxygen.

As shown in Scheme 5, these photooxidations presumably proceed by an initial electron transfer (either by the excited photosensitiser or by singlet oxygen) as shown in the following sequence. The photooxygenation may involve energy transfer between excited triplet MB and molecular oxygen. The triplet sensitiser converts ground-state oxygen into a short-lived and highly reactive species. A non-ambiguous singlet oxygen oxidation of some tertiary amines has previously been reported for such species.[15] However, photooxygenation could also proceed *via* a first electron transfer from the electron donor to the excited MB. The radical anion $MB^{-\bullet}$ could be re-oxidised by molecular oxygen to produce the superoxide anion $O_2^{-\bullet}$. The

Table 1 Photooxidation of some symmetrical piperidinic and pyrrolidinic derivatives

Substrate	Photocyanation ($h\nu$/O_2/MB_{cat}/CH_3CN/TMSCN)	Yield [a] (%)	Second photooxidation ($h\nu$/O_2/MB_{cat}/CH_3CN/$\mathbf{H_2O}$)	Yield [b] (%)
 **6**	 **6a**	90	 **6b**	95
 **7**	 **7a**	85	 **7b**	60
 **8**	 **8a**	96	 **8b**	75
 **9**	 **9a**	80	 **9b**	72
 **10**	 **10a**	100	 **10b**	91
 **11**	 **11a**	59	 **11b**	45

[a] Of cyano product without purification before the second photooxidation. [b] After purification on aluminium oxide.

Table 2 Photooxidation of some unsymmetrical piperidinic and pyrrolidinic derivatives

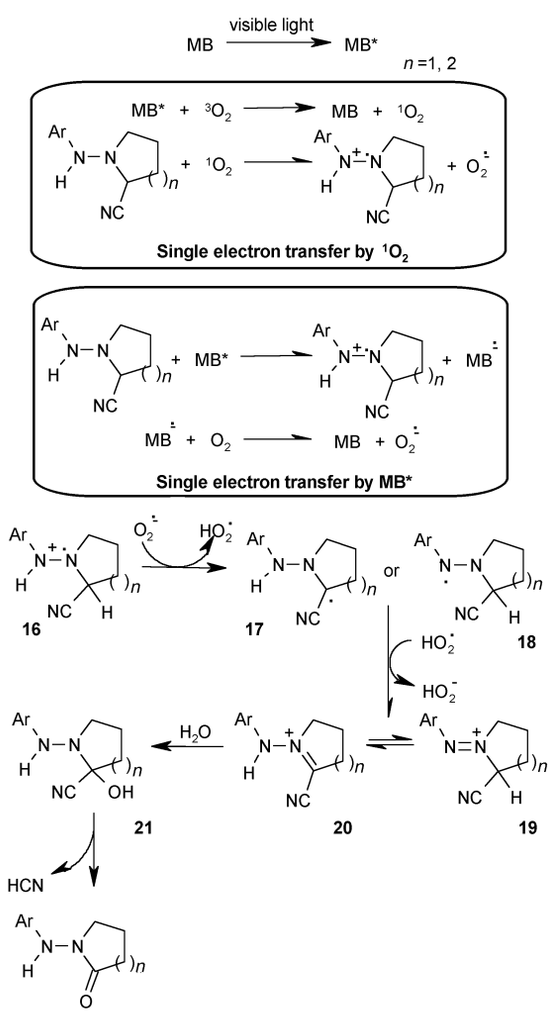
R	Alkylation, yield [a] (%)	Photocyanation ($h\nu$/O_2/MB_{cat}/CH_3CN/TMSCN) Cyano compounds [b] (%)	Second photooxidation ($h\nu$/O_2/MB_{cat}/CH_3CN/$\mathbf{H_2O}$) Lactam [c] (%)
n-C_3H_7	**12**, 74	100	**12a**, 56
i-C_3H_7	**13**, 84	100	**13a**, 34
CH_3	**14**, 72	100	**14a**, 55
$PhCH_2$	**15**, 61	100	**15a**, 55

[a] After purification on aluminium oxide. [b] Yield without purification before the second photooxidation. [c] Yield after separation on aluminium oxide.

reaction between the hydrazinium radical cation and the superoxide anion could lead to oxidation products. Deprotonation of the radical cation **16** by $O_2^{-\bullet}$ should yield the α-hydrazino radical **17** or the hydrazyl radical **18** which could be rapidly oxidised to the hydrazinium alkylidene cation **20**, in tautomeric equilibrium with the 1,1-dialkyl-2-phenyldiazenium **19**. Quenching of **20** by a water molecule should give the cyanohydrin **21** followed by an elimination of HCN leading to the observed hydrazide.

Such a mechanism can be proposed considering the following arguments. The irradiation of the cyano compound **6a** under similar conditions but using anhydrous acetonitrile gives only starting material. This oxidation proceeds exclusively in presence of small amounts of water.

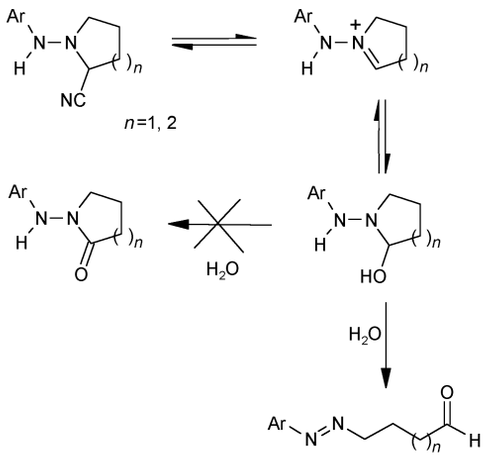
It has previously been reported that lactams can be obtained by photochemical reaction of pyrrolidine compounds by quenching of the iminium ion intermediate by the hydrogen peroxide generated *in situ*. With our conditions, molecular oxygen does not seem to be necessary. Indeed, the irradiation of the α-hydrazinonitrile **8a** under a nitrogen atmosphere with an equivalent of MB gives the corresponding lactam **8b**



Scheme 5

in 75% yield, but the photochemical reaction is extremely slow. However, MB sensitised photooxidation can be performed with a catalytic amount of photosensitiser under an oxygen atmosphere.

Another mechanism could be involved as shown in Scheme 6.



Scheme 6

The cyano product would be in equilibrium with the hydrazinium cation in acetonitrile, which would be rapidly quenched by a small amount of water leading to the α-hydrazinohydroxy derivative, readily oxidised *in situ* to give the corresponding lactam. Such a mechanism can be excluded in the light of previous results recently published.[14] We have demonstrated that the quenching by water of such hydrazinium cations under photooxidation conditions leads to a very efficient nitrogen ring opening reaction. We don't observe any trace of a linear compound. This result seems to indicate that the equilibrium between the α-hydrazinonitrile and the hydrazinium cation doesn't occur.

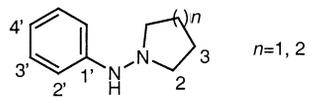
Conclusion

A very similar oxidation of α-aminonitriles to lactams, which also proceeds by single electron transfer and described by Husson and co-workers,[16] involves the presence of a strong base followed by molecular oxygen addition. In our study we have shown that two successive photooxidations of *N*-arylaminopiperidines and *N*-arylaminopyrrolidines give the corresponding lactam products. This transformation occurs by the reaction of an initial hydrazinium cation with cyanide ion as nucleophile followed by reaction with water after a second oxidation. A particularly noteworthy observation is that the second reaction of α-hydrazinonitrile oxidation to lactams proceeds by a photocatalytic process in the presence of oxygen.

Experimental

All materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) and diethyl ether were distilled from benzophenone–sodium prior to use. IR spectra (cm^{-1} with polystyrene calibration, in $CHCl_3$ unless otherwide noted) were recorded on a Perkin-Elmer 457 or on a Philips PU9716 spectrophotometer. ^1H NMR (400 or 300 MHz, in $CDCl_3$, reference TMS, δ_H 0.0) and ^{13}C NMR (100.6 or 75.4 MHz, in $CDCl_3$, reference $CDCl_3$, δ_C 77.0) spectra were recorded on Bruker AM400 or AC300P spectrometers. Chemical shift data are reported in parts per million downfield from TMS, and coupling constants (*J*) in Hz. GC-MS spectra (EI and CI) were recorded on a HP G1019A (70 eV, *m*/*z*) spectrometer. Elemental analyses were performed by the S.I.A.R. (Service Régional de Microanalyse de l'Université Paris VI). HRMS spectra were obtained by the Laboratory of the E.N.S. (Ecole Normale Supérieure de Paris). Flash column and thin-layer chromatography were done by using Aluminium oxid 90 (Merck, act. II-III) or Silica gel 60 (230–400 mesh).

For a better consistency of designation of the NMR signals, the structures have the following numbering systems which are different from the IUPAC one.



General procedure for the cyclic voltammetry

Electrochemical measurements were carried out with an M 273 EGG potentiostat connected to a three-electrode cell. The working electrode was a 0.25 cm^2 platinum wire and the counter electrode was a 2 cm^2 platinum foil. The reference electrode used in this study is an Ag^+/Ag electrode (silver wire//$AgNO_3$ in acetonitrile solution, +0.3 V *vs.* SCE). The supporting electrolyte was 0.5 M NEt_4BF_4 in acetonitrile solution. The potential scan rate in the cyclic voltammetry experiments was 50 mV s^{-1}. The measurements were not corrected from the ohmic drop existing between the working and reference electrode.

Preparation of the hydrazines 6–11

Preparation of the hydrazines **6**–**8**, **11** was previously described,[14] and the structures of these compounds were fully ascertained by complete spectroscopic determination.

Ethyl 4-[(pyrrolidin-1-yl)amino]benzoate 9. According to the typical procedure used for compound **7**, **9** was obtained in 30% yield as an orange solid. IR (neat)/cm^{-1} 2900, 1660, 1585, 1260; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, t, *J* 7.0, CH_3), 1.88 (4H, m, H-2), 2.84 (4H, s, H-3), 4.31 (2H, q, *J* 7.0, OCH_2), 6.86 (2H, d, *J* 8.5, H-2′), 7.87 (2H, d, *J* 8.6, H-3′); ^{13}C NMR (100.6 MHz) δ 14.45 (CH_3), 22.00 (C-3), 55.72 (C-2), 60.24 (OCH_2), 111.81 (C-2′), 120.31 (C-4′), 131.31 (C-3′), 151.52 (C-1′), 166.71 (C=O). HRMS (EI): calc. for $C_{13}H_{18}N_2O_2$ ($M^{+\bullet}$) *m*/*z* 234.1368, obs. 234.1370.

1-[(3-Trifluoromethylphenyl)amino]piperidine 10. According to the typical procedure used for compound **6**, **10** was obtained in 70% yield as a yellow oil. IR (neat)/cm^{-1} 3250, 2940, 1610; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (2H, m, H-4), 1.72 (4H, tt, *J* 5.5, 5.5, H-3), 2.67 (4H, s, H-2), 4.55 (1H, s, NH), 7.01 (2H, m, H-4′, H-6′), 7.15 (1H, s, H-2′), 7.27 (1H, dd, *J* 8.1, 8.1, H-5′); ^{13}C NMR (75.4 MHz) δ 23.42 (C-4), 25.83 (C-3), 57.18 (C-2), 109.55 (C-2′), 115.33 (C-6′), 116.10 (C-4′), 124.25 (q, *J* 3.6, CF_3), 129.31 (C-5′), 131.33 (q, *J* 0.42, C-3′), 148.03 (C-1′). HRMS (EI): calc. for $C_{12}H_{15}N_2F_3$ ($M^{+\bullet}$) *m*/*z* 244.1187, obs. 244.1189.

General procedure for photocyanation of compounds 1, 6–11

A solution of the tertiary amine **1**, or of the hydrazines **6**–**11** (1 mmol), in acetonitrile (20 mL) to which were added TMSCN (270 μL, 2 mmol) and a catalytic amount of MB (4 mg, 0.01 mmol) was irradiated under oxygen bubbling with a 1800 W xenon lamp through a UV cut-off glass filter (λ > 630 nm) at 20 °C. After reaction, monitored by TLC, the resulting mixture was concentrated under reduced pressure to give a blue oil. The crude product was dissolved in 50 mL of 10% Na_2CO_3, followed by 50 mL of CH_2Cl_2. The organic layer was separated and the aqueous solution extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with aqueous Na_2CO_3 (30 mL, 10%), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting cyano product was pure enough for the second photooxidation.

The syntheses of compounds **8a** and **11a** have already been described.[14]

1-Cyclohexylpiperidine-2-carbonitrile 2. According to the typical procedure, compound **2** was obtained after 1 h of irradiation as a yellow oil (92%). IR (neat)/cm^{-1} 2200; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05–2.05 (16H, m), 2.27–2.48 (2H, m, H-6$_{ax}$, H-7), 2.95 (1H, m, H-6$_{eq}$), 4.05 (1H, m, H-2$_{eq}$); ^{13}C NMR (75.4 MHz) δ 20.95, 25.31, 25.40, 25.53, 26.00, 29.70, 29.77, 30.23, 45.75 (C-6), 49.79 (C-2), 62.03 (C-7), 118.44 (CN). MS (CI/NH_3) *m*/*z* (rel. intensity) 193 ($M^+ + 1$, 54), 166 (100). HRMS (CI/NH_3): calc. for $C_{12}H_{21}N_2$ ($M^+ + 1$) *m*/*z* 193.1705, obs. 193.1708.

1-[(4-Nitrophenyl)amino]piperidine-2-carbonitrile 6a. According to the typical procedure, compound **6a** was obtained after 4 h of irradiation as a yellow crystalline solid (90%), mp 148–149 °C. IR (KBr)/cm^{-1} 3280, 2940, 2220, 1600; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52–1.88 (4H, m, H-4, H-5), 2.00–2.09 (2H, m, H-3), 2.76 (1H, ddd, *J* 11.0, 11.0, 3.0, H-6$_{ax}$), 3.03 (1H, dm, *J* 11.1, H-6$_{eq}$), 4.11 (1H, m, H-2$_{eq}$), 5.64 (1H, s, NH), 6.87 (2H, dm, *J* 9.2, H-2′), 8.11 (2H, dm, *J* 9.5, H-3′); ^{13}C NMR (75.4 MHz) δ 19.46 (C-4), 25.08 (C-5), 28.72 (C-3), 52.42 (C-6), 56.10 (C-2), 111.69 (C-2′), 116.40 (CN), 126.19 (C-3′), 140.28 (C-1′), 151.62 (C-4′). MS (CI/NH_3) *m*/*z* (rel. intensity) 265 (17), 264 (100), 247 ($M^+ + 1$, 23). Calc. for $C_{12}H_{14}N_4O_2$: C 58.53; H 5.73; N 22.75. Found: C 58.42; H 5.49; N 22.82%.

1-[(4-Nitrophenyl)amino]pyrrolidine-2-carbonitrile 7a. According to the typical procedure, compound **7a** was obtained after 3 h of irradiation as a green oil (85%). IR (neat)/cm^{-1} 3280, 2960, 2240, 1600; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96–2.16 (2H, m, H-4), 2.17–2.39 (2H, m, H-3), 2.94 (1H, m, H-5$_\alpha$), 3.22 (1H, m, H-5$_\beta$), 4.08 (1H, m, H-2), 5.67 (1H, s, NH), 6.89 (2H, dm, *J* 9.2, H-2′), 8.11 (2H, dm, *J* 9.2, H-3′); ^{13}C NMR (75.4 MHz) δ 20.45 (C-4), 27.44 (C-3), 52.69 (C-5), 53.01 (C-2), 111.31 (C-2′), 117.41 (CN), 126.00 (C-3′), 139.85 (C-1′), 152.60 (C-4′). MS (CI/NH_3) *m*/*z* (rel. intensity) 251 (15), 250 (100), 233 ($M^+ + 1$, 20). HRMS (EI): calc. for $C_{11}H_{12}N_4O_2$ ($M^{+\bullet}$) *m*/*z* 232.0960, obs. 232.0961.

Ethyl 4-[(2-cyanopyrrolidin-1-yl)amino]benzoate 9a. According to the typical procedure, compound **9a** was obtained after 3 h of irradiation as a green oil (80%). IR (neat)/cm^{-1} 3280, 2980, 2220, 1680, 1590; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (3H, t, *J* 7.1, CH_3), 1.96–2.08 (2H, m, H-4), 2.16–2.34 (2H, m, H-3), 2.81 (1H, ddd, *J* 8.7, 8.7, 8.7, H-5$_\alpha$), 3.24 (1H, m, H-5$_\beta$), 4.08 (1H, dd, *J* 7.6, 2.3, H-2), 4.31 (3H, q, *J* 7.1, OCH_2), 5.16 (1H, s, NH), 6.86 (2H, dm, *J* 8.8, H-2′), 7.90 (2H, dm, *J* 8.8, H-3′); ^{13}C NMR (75.4 MHz) δ 14.45 (CH_3), 20.46 (C-4), 27.45 (C-3), 52.53 (C-5), 55.12 (C-2), 60.44 (OCH_2), 111.95 (C-2′), 117.51 (CN), 121.59 (C-4′), 131.39 (C-3′), 150.99 (C-1′), 166.55 (C=O). MS (EI) *m*/*z* (rel. intensity) 259 ($M^{+\bullet}$, 100), 214 (23), 179 (27), 164 (31), 149 (78). HRMS (EI): calc. for $C_{14}H_{17}N_3O_2$ ($M^{+\bullet}$) *m*/*z* 259.1321, obs. 259.1326.

1-[(3-Trifluoromethylphenyl)amino]piperidine-2-carbonitrile 10a. According to the typical procedure, compound **10a** was obtained after 4 h of irradiation as a green oil (100%). IR (neat)/cm^{-1} 3250, 2940, 2220, 1620; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50–1.85 (4H, m, H-4, H-5), 1.98–2.07 (2H, m, H-3), 2.67 (1H, ddd, *J* 11.0, 11.0, 3.0, H-6$_{ax}$), 3.05 (1H, dm, *J* 11.0, H-6$_{eq}$), 4.13 (1H, m, H-2$_{eq}$), 5.04 (1H, s, NH), 7.00 (1H, dm, *J* 7.3, H-6′), 7.07 (1H, dm, *J* 7.7, H-4′), 7.13 (1H, s, H-2′), 7.31 (1H, t, *J* 7.7, H-5′); ^{13}C NMR (75.4 MHz) δ 19.45 (C-4), 25.47 (C-5), 28.59 (C-3), 52.05 (C-6), 56.00 (C-2), 109.78 (C-2′), 116.40 (CN), 116.51 (C-6′), 116.56 (C-4′), 125.59 (q, *J* 3.4, CF_3), 129.69 (C-5′), 131.58 (q, *J* 0.21, C-3′), 146.54 (C-1′). HRMS (EI): calc. for $C_{13}H_{14}N_3F_3$ ($M^{+\bullet}$) *m*/*z* 269.1140, obs. 269.1134.

Alkylations of compound 8a

A general procedure for alkylation of compound **8a** with Grignard reagents was previously described.[14] The compounds **12** and **13** have already been characterised.

Ethyl 4-[(2-methylpiperidin-1-yl)amino]benzoate 14. According to the typical procedure, compound **14** was obtained by alkylation of **8a** with methylmagnesium iodide as an orange solid (72%), mp 70–72 °C. IR (neat)/cm^{-1} 3280, 2940, 1700, 1600; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (3H, d, *J* 6.1, CH_3), 1.21–1.29 (1H, m, H-4), 1.35 (3H, t, *J* 7.1, OCH_2CH_3), 1.39–1.47 (1H, m, H-4), 1.60–1.77 (4H, m, H-3, H-5), 2.23 (1H, ddd, *J* 10.5, 10.5, 4.0, H-6$_{ax}$), 2.31 (1H, m, H-2$_{ax}$), 3.08 (1H, dm, *J* 10.8, H-6$_{eq}$), 4.31 (2H, q, *J* 7.1, OCH_2), 4.62 (1H, s, NH), 6.82 (2H, d, *J* 8.7, H-2′), 7.85 (2H, d, *J* 8.9, H-3′); ^{13}C NMR (75.4 MHz) δ 14.52 (OCH_2CH_3), 19.95 (CH_3), 24.09 (C-4), 25.96 (C-5), 34.24 (C-3), 57.23 (C-6), 60.15 (OCH_2), 61.40 (C-2), 111.18 (C-2′), 119.42 (C-4′), 131.31 (C-3′), 152.89 (C-1′), 166.84 (C=O). MS (EI) *m*/*z* (rel. intensity) 263 (18), 262 ($M^{+\bullet}$, 100), 247 (93), 217 (34), 173 (20), 164 (20), 121 (18), 84 (27). HRMS (EI): calc. for $C_{15}H_{22}N_2O_2$ ($M^{+\bullet}$) *m*/*z* 262.1681, obs. 262.1685.

Ethyl 4-[(2-benzylpiperidin-1-yl)amino]benzoate 15. According to the typical procedure, compound **15** was obtained by alkylation of **8a** with benzylmagnesium chloride as an orange oil (61%). IR (neat)/cm^{-1} 3300, 2940, 1680, 1600; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13–1.20 (1H, m, H-4), 1.37 (3H, t, *J* 7.1, OCH_2CH_3), 1.28–1.40 (1H, m, H-4), 1.59–1.71 (4H, m, H-3, H-5), 2.27 (1H, m, H-6$_{ax}$), 2.44 (2H, m, CH_2Ph), 3.15 (1H, dm, *J* 10.7, H-6$_{eq}$), 3.24 (1H, dm, *J* 9.6, H-2$_{eq}$), 4.32 (2H, q, *J* 7.1, OCH_2), 4.73 (1H, s, NH), 6.87 (2H, d, *J* 8.7, H-2′), 7.10 (2H, dm, *J* 8.3, CH), 7.18 (1H, dm, *J* 7.3, CH), 7.25 (2H, ddm, *J* 7.4, 7.4, CH), 7.89 (2H, d, *J* 8.9, H-3′); ^{13}C NMR (75.4 MHz) δ 14.54 (OCH_2CH_3), 23.84 (C-4), 25.93 (C-5), 31.03 (2-CH_2), 39.89 (C-3), 57.67 (C-6), 60.24 (OCH_2), 67.29 (C-2), 111.58 (C-2′), 119.89 (C-4′), 125.84 (CH), 128.13 (CH), 129.51 (CH), 131.35 (C-3′), 139.68 (C_q), 152.53 (C-1′), 166.84 (C=O). MS (EI) *m*/*z* (rel. intensity) 338 ($M^{+\bullet}$, 25), 293 (24), 248 (37), 247 (100), 217 (29), 201 (12), 173 (31), 164 (20), 108 (15), 91 (24), 84 (13). HRMS (EI): calc. for $C_{21}H_{26}N_2O_2$ ($M^{+\bullet}$) *m*/*z* 338.1994, obs. 338.1993.

Photocyanation of compounds 12–15

The general procedure for these cyanations is similar to the one described for cyano compounds **6**–**11**. The mixture of regioisomers obtained is not separated and the crude mixture is directly photooxidised once again.

General procedure for the photooxidation of the cyano compounds 6a–15a

A solution of the cyano substrate **6a**–**15a** (1 mmol) in acetonitrile (18 mL) and distilled water (2 mL), to which was added a catalytic amount of MB (4 mg, 0.01 mmol), was irradiated under oxygen bubbling with a 1800 W xenon lamp through a UV cut-off glass filter ($\lambda > 630$ nm) at 20 °C. After reaction, monitored by TLC, the resulting mixture was concentrated under reduced pressure to give a blue oil. The crude product was dissolved in 50 mL of 10% Na_2CO_3, followed by 50 mL of CH_2Cl_2. The organic layer was separated and the aqueous solution extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with aqueous Na_2CO_3 (30 mL, 10%), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting mixture was purified by flash chromatography on aluminium oxide.

1-[(4-Nitrophenyl)amino]piperidin-2-one 6b. According to the typical procedure, compound **6b** was obtained after 4 h of irradiation as a brown crystalline solid (95%), mp 116–117 °C. IR (KBr)/cm^{-1} 3240, 2940, 1640, 1585; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76–2.05 (4H, m, H-4, H-5), 2.50 (2H, t, *J* 6.3, H-3), 3.52 (2H, t, *J* 5.8, H-6), 6.56 (2H, dm, *J* 9.1, H-2′), 7.57 (1H, s, NH), 7.95 (2H, dm, *J* 9.3, H-3′); ^{13}C NMR (75.4 MHz) δ 20.93 (C-4), 23.41 (C-5), 32.58 (C-3), 51.51 (C-6), 111.61 (C-2′), 125.72 (C-3′), 140.67 (C-1′), 152.20 (C-4′), 170.55 (C-2). MS

(EI) *m/z* (rel. intensity) 236 (12), 235 ($M^{+\bullet}$, 100), 206 (8), 150 (15), 122 (38), 70 (18), 55 (8). HRMS (EI): calc. for $C_{11}H_{13}N_3O_3$ ($M^{+\bullet}$) *m/z* 235.0957, obs. 235.0955.

1-[(4-Nitrophenyl)amino]pyrrolidin-2-one 7b. According to the typical procedure, compound **7b** was obtained after 3 h of irradiation as a brown crystalline solid (60%), mp 196–197 °C. IR (KBr)/cm^{-1} 3220, 1680, 1580; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (2H, tt, *J* 7.6, 7.6, H-4), 2.46 (2H, t, *J* 7.6, H-3), 3.57 (2H, t, *J* 7.0, H-5), 6.60 (2H, dm, *J* 9.1, H-2′), 7.06 (1H, s, NH), 8.00 (2H, dm, *J* 9.1, H-3′); ^{13}C NMR (75.4 MHz) δ 16.40 (C-4), 28.60 (C-3), 48.09 (C-5), 111.57 (C-2′), 125.79 (C-3′), 140.63 (C-1′), 151.65 (C-4′), 174.45 (C-2). MS (EI) *m/z* (rel. intensity) 222 (12), 221 ($M^{+\bullet}$, 100), 166 (17), 165 (11), 149 (7), 122 (12), 119 (16), 107 (6), 91 (6). HRMS (EI): calc. for $C_{10}H_{11}N_3O_3$ ($M^{+\bullet}$) *m/z* 221.0800, obs. 221.0803.

Ethyl 4-[(2-oxopiperidin-1-yl)amino]benzoate 8b. According to the typical procedure, compound **8b** was obtained after 4 h of irradiation as a yellow oil (75%). IR (neat)/cm^{-1} 3260, 2960, 1700, 1650, 1600; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, t, *J* 7.1, CH_3), 1.83–2.02 (4H, m, H-4, H-5), 2.52 (2H, t, *J* 6.6, H-3), 3.56 (2H, t, *J* 5.9, H-6), 4.30 (2H, q, *J* 7.1, OCH_2), 6.67 (2H, dm, *J* 8.8, H-2′), 7.07 (1H, s, NH), 7.88 (2H, dm, *J* 8.8, H-3′); ^{13}C NMR (100.6 MHz) δ 14.39 (CH_3), 21.19 (C-4), 23.56 (C-5), 32.62 (C-3), 51.47 (C-6), 60.47 (OCH_2), 111.23 (C-2′), 122.73 (C-4′), 131.29 (C-3′), 150.72 (C-1′), 166.39 (C=O), 170.13 (C-2). MS (EI) *m/z* (rel. intensity) 263 (15), 262 ($M^{+\bullet}$, 100), 217 (28), 164 (9), 149 (47), 121 (11), 120 (23), 119 (11), 108 (12), 103 (12), 92 (12), 91 (10). HRMS (EI): calc. for $C_{14}H_{18}N_2O_3$ ($M^{+\bullet}$) *m/z* 262.1317, obs. 262.1316.

Ethyl 4-[(2-oxopyrrolidin-1-yl)amino]benzoate 9b. According to the typical procedure, compound **9b** was obtained after 4 h of irradiation as a brown oil (72%). IR (neat)/cm^{-1} 3240, 3000, 1700, 1605; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, t, *J* 7.1, CH_3), 2.15 (2H, tt, *J* 7.7, 7.7, H-4), 2.49 (2H, t, *J* 7.9, H-3), 3.60 (2H, t, *J* 7.0, H-5), 4.31 (2H, q, *J* 7.1, OCH_2), 6.65 (1H, s, NH), 6.67 (2H, dm, *J* 8.7, H-2′), 7.88 (2H, dm, *J* 8.7, H-3′); ^{13}C NMR (75.4 MHz) δ 14.41 (CH_3), 16.49 (C-4), 28.85 (C-3), 48.09 (C-5), 60.54 (OCH_2), 112.00 (C-2′), 122.68 (C-4′), 131.32 (C-3′), 150.07 (C-1′), 166.36 (C=O), 174.29 (C-2). MS (EI) *m/z* (rel. intensity) 249 (16), 248 ($M^{+\bullet}$, 100), 220 (13), 203 (27), 192 (12), 164 (17), 149 (22), 86 (18), 84 (28). HRMS (EI): calc. for $C_{13}H_{16}N_2O_3$ ($M^{+\bullet}$) *m/z* 248.1161, obs. 248.1160.

1-[(3-Trifluoromethylphenyl)amino]piperidin-2-one 10b. According to the typical procedure, compound **10b** was obtained after 4 h of irradiation as a yellow crystalline solid (91%), mp 144–145 °C. IR (KBr)/cm^{-1} 3240, 2960, 1630, 1580; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87–2.08 (4H, m, H-4, H-5), 2.57 (2H, t, *J* 6.4, H-3), 3.61 (2H, t, *J* 5.9, H-6), 6.87–7.01 (2H, m, H-6′, H-4′), 7.15 (1H, d, *J* 7.8, H-2′), 7.33 (1H, t, *J* 8.0, H-5′); ^{13}C NMR (75.4 MHz) δ 21.08 (C-4), 23.40 (C-5), 32.38 (C-3), 51.26 (C-6), 109.98 (C-2′), 116.58 (C-6′), 117.78 (C-4′), 123.92 (q, *J* 3.6, CF_3), 129.65 (C-5′), 131.50 (q, *J* 0.21, C-3′), 147.119 (C-1′), 170.03 (C-2). HRMS (CI/CH_4): calc. for $C_{12}H_{14}N_2OF_3$ ($M^+ + 1$) *m/z* 259.1058, obs. 259.1055.

4-Methyl-1-(phenylamino)piperidin-2-one 11b. According to the typical procedure, compound **11b** was obtained after 4 h of irradiation as a green oil (45%). IR (neat)/cm^{-1} 3260, 2950, 1660, 1600; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (3H, d, *J* 6.3, CH_3), 1.62–1.80 (2H, m, H-4, H-5), 1.94–2.22 (2H, m, H-5, H-6), 2.61 (1H, ddd, *J* 16.3, 4.2, 2.2, H-6), 3.56–3.63 (2H, m, H-3), 6.76 (2H, dm, *J* 8.4, H-2′), 6.92 (1H, tt, *J* 7.4, 1.1, H-4′), 7.24 (2H, ddm, *J* 8.4, 7.4, H-3′); ^{13}C NMR (75.4 MHz) δ 20.92 (CH_3), 28.04 (C-4), 31.21 (C-5), 40.42 (C-3), 50.00 (C-6), 114.00 (C-2′), 121.52 (C-4′), 129.29 (C-3′), 146.60 (C-1′), 169.46 (C-2). MS (EI) *m/z* (rel. intensity) 205 (14), 204 ($M^{+\bullet}$, 100), 133 (6), 106 (8), 105 (19), 93 (25), 92 (27), 84 (12), 77 (40), 65 (15). HRMS (EI): calc. for $C_{12}H_{16}N_2O$ ($M^{+\bullet}$) *m/z* 204.1263, obs. 204.1264.

Ethyl 4-[(2-oxo-6-propylpiperidin-1-yl)amino]benzoate 12a. According to the typical procedure, compound **12a** was obtained after 5 h of irradiation as a yellow oil (56%). IR (neat)/cm^{-1} 3260, 2970, 1700, 1650, 1600; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* 7.3, CH_3), 1.16–1.55 (4H, m, 6CH_2CH_2), 1.35 (3H, t, *J* 7.1, OCH_2CH_3), 1.75–1.98 (3H, m, H-4, H-5), 2.05–2.14 (1H, m, H-5), 2.51 (2H, m, H-3), 3.59 (1H, m, H-6), 4.31 (2H, q, *J* 7.1, OCH_2), 6.69 (1H, s, NH), 6.72 (2H, dm, *J* 8.8, H-2′), 7.90 (2H, dm, *J* 8.8, H-3′); ^{13}C NMR (100.6 MHz) δ 14.03 (CH_3), 14.41 (OCH_2CH_3), 17.79 (6CH_2CH_2), 19.24 (C-4), 27.02 (6-CH_2), 32.63 (C-5), 34.74 (C-3), 60.45 (OCH_2), 60.56 (C-6), 112.41 (C-2′), 122.76 (C-4′), 131.27 (C-3′), 151.49 (C-1′), 166.40 (C=O), 170.61 (C-2). MS (EI) *m/z* (rel. intensity) 305 (20), 304 ($M^{+\bullet}$, 100), 259 (23), 180 (48), 169 (23), 165 (26), 149 (16). HRMS (EI): calc. for $C_{17}H_{24}N_2O_3$ ($M^{+\bullet}$) *m/z* 304.1787, obs. 304.1782.

Ethyl 4-[(6-isopropyl-2-oxopiperidin-1-yl)amino]benzoate 13a. According to the typical procedure, compound **13a** was obtained after 7 h of irradiation as a yellow oil (34%). IR (neat)/cm^{-1} 3260, 2970, 1700, 1650, 1600; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (3H, d, *J* 6.8, CH_3), 0.91 (3H, d, *J* 7.1, CH_3), 1.35 (3H, t, *J* 7.1, OCH_2CH_3), 1.62–1.85 (3H, m, H-4, CH), 1.92–2.05 (2H, m, H-5), 2.41 (1H, m, H-3), 2.60 (1H, dm, *J* 17.6, H-3), 3.66 (1H, m, H-6), 4.31 (2H, q, *J* 7.1, OCH_2), 6.66 (1H, s, NH), 6.69 (2H, dm, *J* 8.7, H-2′), 7.90 (2H, dm, *J* 8.7, H-3′); ^{13}C NMR (100.6 MHz) δ 14.43 (OCH_2CH_3), 15.77 (CH_3), 18.84 (CH_3), 19.06 (C-4), 23.00 (C-5), 28.84 (6-CH), 32.93 (C-3), 60.47 (OCH_2), 64.34 (C-6), 112.29 (C-2′), 122.52 (C-4′), 131.32 (C-3′), 151.16 (C-1′), 166.42 (C=O), 171.60 (C-2). MS (EI) *m/z* (rel. intensity) 305 (21), 304 ($M^{+\bullet}$, 100), 302 (24), 262 (42), 259 (93), 233 (17), 189 (17), 180 (57), 169 (17), 164 (28), 149 (24). HRMS (EI): calc. for $C_{17}H_{24}N_2O_3$ ($M^{+\bullet}$) *m/z* 304.1787, obs. 304.1789.

Ethyl 4-[(6-methyl-2-oxopiperidin-1-yl)amino]benzoate 14a. According to the typical procedure, compound **14a** was obtained after 8 h of irradiation as a yellow oil (55%). IR (neat)/cm^{-1} 3260, 2970, 1700, 1650, 1610; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, d, *J* 6.4, CH_3), 1.33 (3H, t, *J* 7.1, OCH_2CH_3), 1.70–1.98 (3H, m, H-4, H-5), 2.05–2.16 (1H, m, H-5), 2.50 (2H, m, H-3), 3.75 (1H, m, H-6), 4.29 (2H, q, *J* 7.1, OCH_2), 6.67 (2H, dm, *J* 8.7, H-2′), 6.91 (1H, s, NH), 7.86 (2H, dm, *J* 8.7, H-3′); ^{13}C NMR (100.6 MHz) δ 14.41 (OCH_2CH_3), 18.01 (CH_3), 19.64 (C-4), 30.49 (C-5), 32.79 (C-3), 56.51 (C-6), 60.46 (OCH_2), 112.19 (C-2′), 122.30 (C-4′), 131.20 (C-3′), 151.54 (C-1′), 166.45 (C=O), 170.77 (C-2). MS (EI) *m/z* (rel. intensity) 277 (18), 276 ($M^{+\bullet}$, 100), 231 (18), 180 (15), 149 (35), 86 (35), 84 (52), 51 (22). HRMS (EI): calc. for $C_{15}H_{20}N_2O_3$ ($M^{+\bullet}$) *m/z* 276.1474, obs. 276.1478.

Ethyl 4-[(6-benzyl-2-oxopiperidin-1-yl)amino]benzoate 15a. According to the typical procedure, compound **15a** was obtained after 7 h of irradiation as a yellow oil (55%). IR (neat)/cm^{-1} 3260, 2960, 1700, 1650, 1600; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, t, *J* 7.1, OCH_2CH_3), 1.74–1.83 (2H, m, H-4), 1.85–2.03 (2H, m, H-5), 2.55 (2H, m, H-3), 2.67 (1H, dd, *J* 13.1, 10.5, 6-CH_2), 3.35 (1H, dd, *J* 13.2, 3.6, 6-CH_2), 3.80 (1H, m, H-6), 4.32 (2H, q, *J* 7.1, OCH_2), 6.73 (2H, dm, *J* 8.8, H-2′), 7.07 (1H, s, NH), 7.11 (2H, dm, *J* 6.8, *o*-CH), 7.21 (1H, dm, *J* 7.2, *p*-CH), 7.26 (2H, ddm, *J* 7.5, 6.8, *m*-CH), 7.91 (2H, dm, *J* 8.7, H-3′); ^{13}C NMR (100.6 MHz) δ 14.45 (CH_3), 17.40 (C-4), 26.09 (C-5), 32.67 (C-3), 38.90 (6-CH_2), 60.50 (OCH_2), 62.23 (C-6), 112.38 (C-2′), 122.67 (C-4′), 126.64 (CH), 128.64 (CH), 129.21 (CH), 131.32 (C-3′), 137.76 (C_q), 151.31 (C-1′), 166.43 (C=O), 170.63 (C-2). MS (EI) *m/z* (rel. intensity) 352 ($M^{+\bullet}$, 75),

307 (25), 261 (100), 233 (28), 215 (21), 164 (35), 149 (42), 100 (21), 91 (31), 84 (26). HRMS (EI): calc. for $C_{21}H_{24}N_2O_3$: ($M^{+\bullet}$) *m*/*z* 352.1787, obs. 352.1793.

References

1 J. Santamaria, M. T. Kaddachi and J. Rigaudy, *Tetrahedron Lett.*, 1990, **31**, 4735.
2 J. Santamaria and M. T. Kaddachi, *Synlett*, 1991, **10**, 739.
3 J. Santamaria, M. T. Kaddachi and C. Ferroud, *Tetrahedron Lett.*, 1992, **33**, 781.
4 C. Ferroud, E. L. Cavalcanti de Amorim, L. Dallery and J. Santamaria, *Synthesis*, 1994, **3**, 291.
5 P. Potier, *Rev. Latinoam. Quim.*, 1978, **9**, 47.
6 D. S. Grierson, in *Organic Reactions*, ed. L. A. Paquette, Wiley and Sons, New York, 1990, vol. 39, p. 85.
7 S. Michel, E. Le Gall, J. P. Hurvois, C. Moinet, A. Tallec, P. Uriac and L. Toupet, *Liebigs Ann. Chem.*, 1997, 259.
8 E. Le Gall, J. P. Hurvois, T. Renaud, C. Moinet, A. Tallec, P. Uriac, S. Sinbandhit and L. Toupet, *Liebigs Ann. Chem.*, 1997, 2089.
9 D. Herlem, Y. Hubert-Brierre, F. Khuong-Huu and R. Goutarel, *Tetrahedron*, 1973, **29**, 2195.
10 F. Khuong-Huu, D. Herlem and Y. Hubert-Brierre, *Tetrahedron Lett.*, 1975, **6**, 359.
11 S. F. Nelsen, V. Peacock and G. R. Weisman, *J. Am. Chem. Soc.*, 1976, **98**, 5269.
12 S. F. Nelsen, D. T. Rumack and M. Meot-Ner, *J. Am. Chem. Soc.*, 1988, **110**, 7945.
13 C. Ferroud, G. Cocquet and A. Guy, *Tetrahedron Lett.*, 1999, **40**, 5005.
14 C. Ferroud, G. Cocquet and A. Guy, *Tetrahedron*, 2000, **56**, 2975.
15 C. Ferroud, P. Rool and J. Santamaria, *Tetrahedron Lett.*, 1998, **39**, 9423.
16 D. S. Grierson, M. Urrea and H. P. Husson, *Heterocycles*, 1985, **23**, 2493; J. Royer and H. P. Husson, *Heterocycles*, 1993, **36**, 1493.