Photochemically Induced Electron Transfer from Aniline Derivatives to Pyridine-2,4-dicarbonitrile: Synthetic and Mechanistic Aspects

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A study on the photochemically induced electron transfer from substituted aniline donors to a 2,4-dicyanopyridine acceptor permits the synthesis of new amino derivatives of the pyridine and forms the basis of a hypothesis on the mechanism of the reaction and the influence of the substituent on the aniline ring.

In a recent paper from our laboratory, a study on a photochemically induced reaction which can be explained by electron transfer from primary or secondary aliphatic amines to pyridine-2,4-dicarbonitrile was reported.[1]

Following photoexcitation of the pyridine and the transfer of the electron (Scheme 1), the resulting two charged species react along different paths. The amino radical cation loses a proton and forms an aminyl radical while the pyridinyl radical anion may undergo two competitive processes involving either reduction to pyridine-2-carbonitrile or substitution of a cyano group with the aminyl radical, to yield, after rearomatization, the amino(cyano)pyridine. The relative amount of reduction *vs.* substitution and the relative ratio of cyano substitution at position 2 or 4 depends on the structure of the amine.

In an effort to understand the synthetic value of this reaction, the mechanism that results in reduction, and the selectivity in substitution, we enlarged this photoinduced electron-transfer reaction to include *meta*- and *para*-substituted anilines as donors. In many aspects this system is more complex than that involving the aliphatic amines, since the absorption bands of aniline lie in the same spectral range as those of the pyridine, and the singlet and triplet energies may lie at levels higher or lower than those of the heterocyclic base.

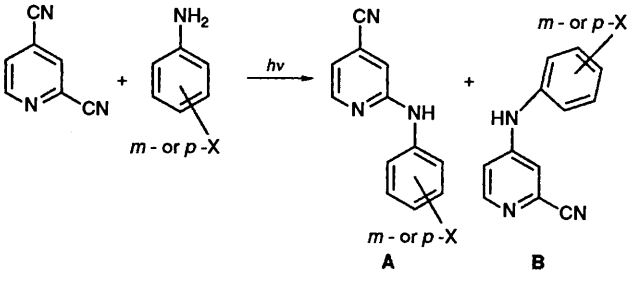
Results and Conclusions

In Scheme 2 and Table 1 the yields obtained and ratios of isomers formed are reported for the substituted anilines that were used in the study and the structural assignments are given in the Experimental section (Table 3). In all the cases studied, there was detected no trace of pyridine-2-carbonitrile, which is always formed, and is generally the principal product formed with aliphatic amines. Considering that there is no loss of material (in all the cases the unchanged pyridine was recovered quantitatively), it may be concluded that pyridine-2-carbo-

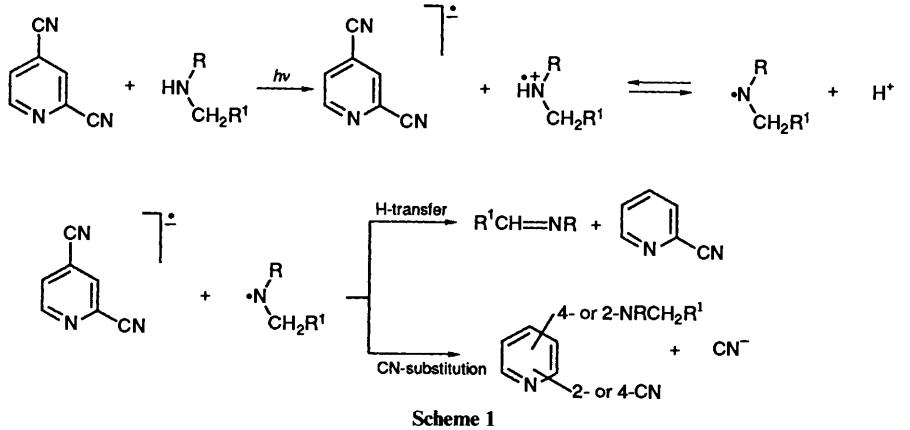
Table 1 Chemical yields and isomer ratios for the substituted anilines[a]

Aniline	X	Yield (%)[b]	A:B[c]	
1	H	27	1.1	
2	*m*-Me	33	1.0	
3	*p*-Me	61	0.9	
4	*m*-OMe	44	1.1	
5	*p*-OMe	30	0.4	
6	*m*-F	31	1.1	
7	*p*-F	19	1.2	
8	*m*-CN	32	2.5	
9	*p*-CN	43	2.0	
10	NHMe	16	1.4	2CNPy (30%)

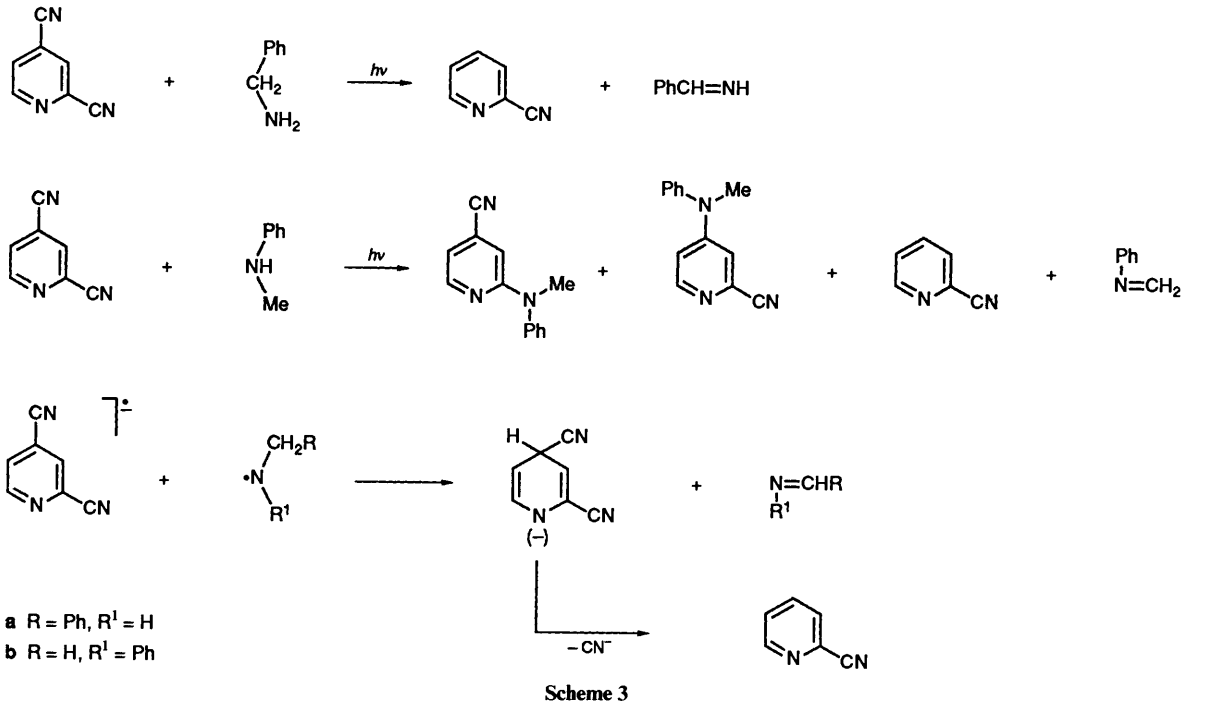
[a] Pyridine-2,4-dicarbonitrile (1 mmol), aniline (1 mmol) and acetonitrile (20 cm^3) degassed and irradiated at λ 254 nm for 4 h. [b] Yields are based on isolated products and are accurate to ± 1%. Ratios were determined by GC and are accurate to ± 0.1. [c] **A** and **B** refer to the isomer indicated in Scheme 1.



Scheme 2



Scheme 1



Scheme 3

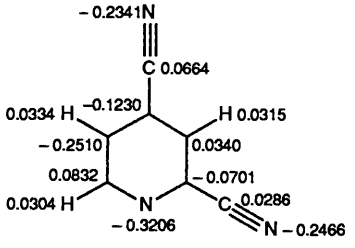


Fig. 1 STO-3G *ab initio* calculations of the electronic densities for the pyridine-2,4-dicarbonitrile radical anion

nitrile is not obtained by a spontaneous loss of CN^- from the pyridine radical anion, but that reduction involves the participation of aminic species implied in the reaction. Only if a hydrogen is carried on the carbon atom α to the aminic radical is it possible to have hydrogen transfer to the pyridine radical anion with formation of an imino derivative. To test this hypothesis two further reactions were run in which pyridine-2,4-dicarbonitrile was irradiated firstly in the presence of benzylamine and secondly with *N*-methylaniline. In the first case two products, benzylimine (inferred since benzaldehyde was obtained after hydrolytic work-up) and pyridine-2-carbonitrile, were formed (Scheme 3). Considering that the benzylaminyl radical can transfer hydrogen easily, pyridine-2-carbonitrile formation is, by far, the favoured process rather than cyano substitution. In the second case, along with the substitution products, pyridine-2-carbonitrile is also formed, confirming once more that only in cases in which there is a hydrogen atom on a carbon α to the aminyl radical can reduction take place (Scheme 3). What is not apparent from the data in Table 1 is any correlation between reactivity and the substituents on the aniline ring. This is due to the fact that only a fraction of the incident light is absorbed by the pyridine, the remaining part being absorbed by the aniline. Considering that the reaction takes place with an electron transfer from the aniline to the excited pyridine, the latter may be obtained either by direct excitation or, if the energetics of an energy transfer is favourable, either from the singlet or the triplet state, *via* a photochemical sensitization. Otherwise the only function of the aniline would be to serve as a screen for the absorption of light by the pyridine. Indeed, the absorption spectra of pyridine-2,4-dicarbonitrile and those of aniline, *p*-cyano- and *p*-methylaniline show the overlapping of their bands. In the case of aniline, which has singlet and triplet energies (E_s 97 kcal mol^{-1} * and E_t 77 kcal mol^{-1})[2] both higher than those of the pyridinedicarbonitrile (E_s 89 kcal mol^{-1}, E_t 64 kcal mol^{-1}),[3] we should expect that energy can be transferred from either excited state of the aniline to the pyridine. The amount of pyridine converted, related to the amount of aniline used, was hence determined. The trend shows that, when most of the light is absorbed by the aniline, there is a decrease in the amount of the pyridine converted, to a point at which the rate of decrease became zero (Table 2).

Another point of interest involves the selectivity displayed by the substituents at position 2 or 4. Considering that the higher electron density for the radical anion is in position 4, (Fig. 1) one should expect that substitution at this position should be favoured. It can be seen in Table 1 that the substitution ratio between the two positions is clearly dependent on the substituent on the benzene ring of the aniline derivative. This trend should be explained by considering that this regioisomer distribution depends on the reversibility of the intermediate that is formed after radical addition. This reversibility effect was already noted in the radical addition to the heterocyclic bases by Minisci;[4] in our case we can consider the difference in energy between the bond N_{anil}–C_{pyr} *vs.* C_{pyr}–CN that must be broken in the intermediate to obtain the final product. (Fig. 2).

The substituent could play an important role increasing or decreasing the N_{anil}–C_{pyr} bond energy in such a way that the cyano group is eliminated instead. The intermediate then reverts back to the anilinyl radical and to the pyridyl radical anion both of which are stabilized. Cross-coupling on the other position would give rise to the final isomer distribution. Another effect that could explain this distribution come from the consideration that the distance at which the electron transfer occurs will vary depending on the substituent; the more electron donating is the substituent, the farther apart the molecules can be during the electron-transfer process. For this reason we examined the possibility of a correlation between the ionization potential of

* 1 cal = 4.184 J.

Table 2 Amount of anilinocyanopyridine obtained in comparison with the ratio of aniline:pyridine and the amount of light absorbed by the aniline[a]

Aniline:Pyridine	Light absorbed by the aniline (%)	Pyridine converted (mmol)
1	62	0.21
1.5	71	0.17
2	75	0.10
3	83	0.09
4	86	0.07
5	89	0.07

[a] Solution of pyridine-2,4-dicarbonitrile (0.15 mol dm^{-3}; 5 cm^3) and different amount of a solution aniline (0.75 mol dm^{-3}) to obtain the reported ratios, and acetonitrile to obtain a final volume of 40 cm^3.

Fig. 2 Intermediates of the addition of the anilino radical onto the pyridine-2,4-dicarbonitrile radical anion

the anilines * and the ratio **A**:**B**. As can be seen from our results, this correlation was good for the *para*-substituted series (Fig. 3), which may suggest that a key role is played by the distance at which the electron transfer occurs; the closer the aniline must approach to transfer the electron to the excited heterocyclic base, the higher is the possibility that the substitution will occur in position 2, while the farther apart the molecules are at the time of the transfer the higher is the amount of substitution in position 4.

Experimental

Aniline and its derivatives, which are commercially available, were distilled under nitrogen or crystallized from the appropriate solvent.

Gas chromatographic analyses were performed on a Dani 3800 gas chromatograph using a 2 m glass column (i.d. 2 mm) packed with 10% UCC-W 982 on chrom. W-AW-DMCS and temperature-programmed from 120 to 235 (8° min^{-1} after the first 4 min) using a flame ionization detector. NMR spectra were run on a Varian EM 390 90 MHz spectrometer and chemical shifts are reported in ppm relative to TMS [$(CH_3)_4Si$] as internal standard, J values are given in Hz. The solvent was $CDCl_3$ except where otherwise stated. Mass spectra were run on a RMU 6D single focusing spectrometer. Melting points are uncorrected.

In a typical experiment pyridinedicarbonitrile (0.129 g, 1 mmol) was dissolved in acetonitrile (20 cm^3) and the appropriate aniline derivative (1 mmol) was added. The resulting solution

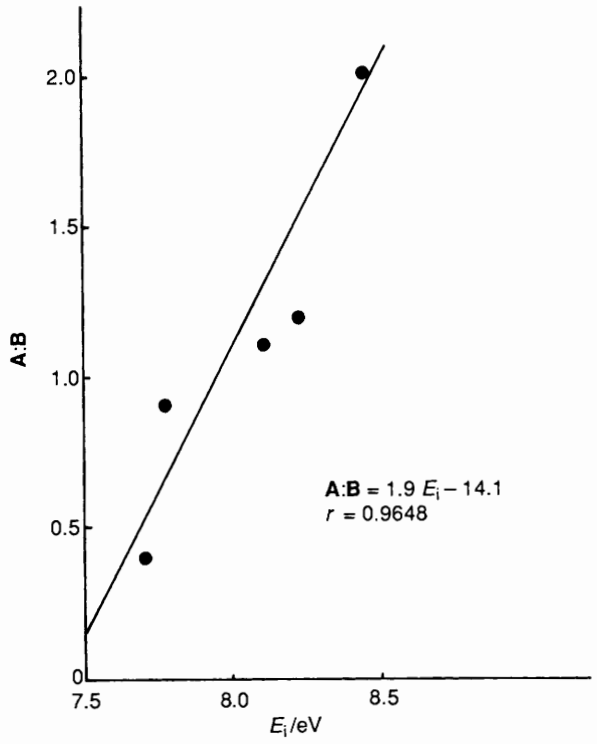


Fig. 3 Correlation between the ratio of the regioisomer distribution *vs.* the ionization potentials of the *para*-substituted anilines

was degassed by bubbling N_2 through it for 20 min and then irradiated in a quartz vessel in a Rayonet RPR-100 equipped with 16 low-pressure mercury lamps irradiating at λ = 254 nm. The solvent was removed under reduced pressure, and the resulting mixture was either analysed by GLC or separated by standard flash chromatography [8] on Merck silica gel (0.040–0.063 mesh) using different mixtures of hexane–ethyl acetate. The order of elution is **A**, aniline, pyridinedicarbonitrile and **B**. The physical properties are reported in Table 3.

The structures of the regioisomers were assigned on the basis that the corresponding derivatives with the aliphatic amines, for which the structures of the regioisomers were determined unquestionably, have physical properties and behaviour similar to those of the anilino derivatives. Based on this fact, we should expect that in the reaction with aniline the product, isomer **1B**, should correspond to 4-anilino-2-cyanopyridine; because its m.p. and ^1H NMR spectrum are coincident with the only product of this class reported in literature,[9] to which the same structure was given, our assignment turned out to be correct. Since the ^1H NMR spectroscopic chemical shifts for each class of regioisomer appear to be characteristic, together with the mass fragmentation and their chromatographic behaviour, we could then assign the correct structures to all the regioisomers.

When benzylamine was used, pyridine-2-carbonitrile was isolated and benzylimine was hydrolysed to benzaldehyde and identified by comparison with an authentic sample.

In the case of *N*-methylaniline, the imino derivative that is formed is hydrolysed by the silica during the chromatography and was identified as aniline.

The reactions with different amounts of aniline were run, making two stock solutions in acetonitrile: the first of pyridine-2,4-dicarbonitrile (0.15 mol dm^{-3}) and the second of aniline (0.75 mol dm^{-3}); six quartz tubes were filled with the first solution (5 cm^3) and different amounts of the second solution were added in such a way that the molar ratios were, respectively, 1:1, 1.5, 2, 3, 4, 5. The total volumes were adjusted to 40 cm^3 and the solutions degassed for 20 min then irradiated in the Rayonet reactor equipped with a merry-go-round for 1 h. At

* It is difficult to find the whole series of ionization potentials (E_i) for the aniline derivatives we are interested in, determined by the same authors. We found the highest number of E_i values in ref. 5 but the derivative with a cyano group is missing. The value we used is the average of two values found from the correlation of the reported E_i *vs.* the σ^+ values [6] [10 points; r = 0.8788; E_i = 0.496; σ^+ + 8.07; σ^+ (CN) = 0.67 E_i(CN) = 8.40 eV] and from the correlation of the E_i values of the substituted anilines *vs.* E_i values of the corresponding substituted benzenes [7] [7 points; r = 0.9244; $E_{i(aniline)}$ = 0.58 $E_{i(benzene)}$ + 2.55; $E_{i(PhCN)}$ = 10.09 eV; $E_{i(pCNaniline)}$ = 8.52 eV].

Table 3 Spectroscopic data and elemental analyses of cyano- and anilino-pyridines

Compound	M.p./°C	*m/z* (%)	δ_H(ppm)[a]	Found (Required %) C	H	N
A1[b]	136–137	195 (51), 194 (100), 103 (4), 92 (7)	8.20 (1 H, d, J_{6-5} 6 H-6), 7.60–7.00 (6 H, m, 5Har + NH), 6.94 (1 H, d, J_{3-5} 3 H-3), 6.80 (1 H, dd, J_{5-3} 3, J_{5-6} 6 H-5)			
B1	128–130	195 (100), 194 (44), 167 (17), 140 (7)	8.28 (1 H, d, H-6), 7.60–7.00 (5 H, m, 5Har), 7.05 (1 H, d, H-3), 6.90 (1 H, dd, H-5), 6.45 (1 H, bs, NH)	74.0 (73.8)	4.6 (4.65)	21.4 (21.5)
A2	119–121	209 (57), 208 (100), 105 (10), 77 (9)	8.22 (1 H, d, H-6), 7.35–6.85 (6 H, m, 4Har + NH + H-3), 6.80 (1 H, d, H-5), 2.40 (3 H, s, Me)	74.7 (74.6)	5.3 (5.5)	20.0 (20.1)
B2	117–119	209 (100), 208 (27), 194 (12), 181 (10)	8.22 (1 H, d, H-6), 7.40–6.78 (7 H, m, 7Har + NH + H-3 + H-5), 2.38 (3 H, s, Me)	74.75	5.3	20.0
A3	158–159	209 (62), 208 (100), 103 (15), 91 (13), 77 (17)	8.21 (1 H, d, H-6), 7.37–7.00 (5 H, m, 4Har + NH), 6.88 (1 H, d, H-3), 6.78 (1 H, dd, H-5), 2.33 (3 H, s, Me)	74.8	5.35	19.9
B3	124–125	209 (100), 208 (44), 91 (33)	8.21 (1 H, d, H-6), 7.20–6.90 (5 H, m, 4Har + H-3), 6.80 (1 H, dd, H-5), 6.60 (1 H, bs, NH), 2.40 (3 H, s, Me)	74.5	5.3	20.2
A4	87–90	225 (63), 224 (100), 209 (22), 129 (63), 103 (16)	8.28 (1 H, d, H-6), 7.45–6.60 (7 H, m, Har + NH + H-3 + H-5), 3.80 (3 H, s, OMe)	69.2 (69.3)	4.9 (4.9)	18.8 (18.7)
B4	77–79	225 (100), 224 (12), 209 (7), 196 (12), 143 (15), 103(8)	8.22 (1 H, d, H-6), 7.40–6.60 (7 H, m, 4Har + NH + H-3 + H-5), 3.78 (3 H, s, OMe)	69.3	5.0	18.7
A5	132–134	225 (100), 224 (40), 210 (85), 103 (24)	8.22 (1 H, d, H-6), 7.20 and 6.90 (4 H, d, 4Har, J_{a-b} 7.5), 6.80–6.70 (2 H, m, H-3 and H-5), 6.70 (1 H, bs, NH), 3.80 (3 H, s, OMe)	69.4	4.9	18.6
B5	125–127	225 (100), 210 (100)	8.22 (1 H, d, H-6), 7.22–6.80 (5 H, m, 4Har + H-3), 6.70 (1 H, dd, H-5), 6.60 (1 H, bs, NH), 3.85 (3 H, s, OMe)	69.25	5.0	18.6
A6	178–179	213 (51), 212 (100), 92 (19)	DMSO; 8.85 (1 H, bs, NH), 8.28 (1 H, d, H-6), 7.80–6.50 (4 H, m, 4Har), 7.10 (1 H, d, H-3), 6.85 (1 H, dd, H-5)	67.8 (67.6)	3.8 (3.8)	19.6 (19.7)
B6	168–169	213 (100), 212 (31), 185 (9), 158 (2)	DMSO; 8.85 (1 H, bs, NH), 8.23 (1 H, d, H-6), 7.52–6.68 (6 H, m, 4Har + H-3 + H-5)	67.4	3.8	19.8
A7	175–176	213 (61), 212 (100), 92 (22)	8.80 (1 H, bs, NH), 8.27 (1 H, d, H-6), 7.49 (2 H, m, 2Har, J_{a-b} 8.8, J_{a-F} 4.9), 7.05 (2 H, m, 2Har, J_{b-a} 8.8 J_{b-F} 8.3), 6.97 (1 H, d, H-3), 6.83 (1 H, dd, H-5)	67.5	3.8	19.9
B7	149–150	213 (100), 212 (22), 185 (13), 83 (16)	8.28 (1 H, d, H-6), 7.20 (2 H, m, 2Har, J_{a-b} 8.8, J_{a-F} 4.2), 7.08 (2 H, m, 2Har, J_{b-a} 8.8 J_{b-F} 9.0), 7.06 (1 H, d, H-3), 6.84 (1 H, dd, H-5), 6.65 (1 H, bs, NH)	67.7	3.8	19.65
A8	186–189	220 (42), 219 (100)	CD_3COCD_3; 9.00 (1 H, bs, NH), 8.45 (1 H, d, H-6), 8.40–7.25 (4 H, m, 4Har), 7.20 (1 H, d, H-3), 7.10 (1 H, dd, H-5)	71.1 (70.9)	3.6 (3.7)	25.3 (25.4)
B8	207–208	220 (100), 219 (22), 192 (11), 118 (11), 102 (5)	CD_3COCD_3; 8.80 (1 H, br s, NH), 8.38 (1 H, d, H-6), 7.78–7.42 (5 H, m, 4Har + H_3), 7.22 (1 H, dd, H_5)	70.7	3.7	25.7
A9	244–246	220 (55), 219 (100), 102 (12), 92 (9)	CD_3COCD_3; 9.15 (1 H, bs, NH), 8.50 (1 H, d, H-6), 7.95–7.65 (4 H, d, 4Har, J_{a-b} 9), 7.21 (1 H, d, H-3), 7.17 (1 H, dd, H-5)	70.8	3.7	25.5
B9	218–219	220 (100), 219 (79), 192 (13), 165 (7), 102 (7), 76 (11)	CD_3COCD_3; 8.90 (1 H, bs, NH), 8.42 (1 H, d, H-6), 7.78–7.50 (4 H, d, 4Har, J_{a-b} 9), 7.51 (1 H, d, H-3), 7.30 (1 H, dd, H-5)	70.8	3.6	25.6
A10	Oil	209 (44), 208 (100), 193 (11), 106 (34), 104 (17), 91 (11)	8.29 (1 H, d, H-6), 7.60–7.20 (5 H, m, 4Har), 6.71 (1 H, d, H_3), 6.60 (1 H, dd, H-5), 3.50 (3 H, s, NMe)	74.8 (74.6)	5.3 (5.3)	19.9 (20.1)
B10	Oil	209 (100), 208 (69), 193 (15), 77 (35)	8.21 (1 H, d, H-6), 7.60–7.10 (5 H, m, 5Har), 6.85 (1 H, d, H-3), 6.62 (1 H, dd, H-5), 3.32 (3 H, s, NMe)	74.8	5.25	19.9

[a] For solution in $CDCl_3$, except where otherwise stated. H-3, H-5 and H-6 refer to the hydrogen atoms on the pyridine ring. Their coupling constants are the same for all the derivatives and were reported only for the first product. a and b refer to the aromatic protons, respectively, and *ortho* and *meta* to the aminic nitrogen, where it was possible to determine. *J* values are given in Hz. [b] See ref. 9.

the end of the irradiation time benzophenone was added as internal standard, the solvent was evacuated, and the reaction mixtures were examined by GLC.

Theoretical calculations at the STO-3G level were performed using the GAUSSIAN 80 software.

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