A Study of the Photochemically Induced Reaction of Pyridine-2,4-dicarbonitrile with Primary and Secondary Amines. A Direct Synthesis of Aminocyanopyridines

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A novel synthesis of alkylaminopyridinecarbonitriles by a photoinitiated substitution reaction between pyridine-2,4-dicarbonitrile and certain amines is described. The mechanism is discussed.

Aminopyridines have found broad applications as pharmaceuticals,[1] bactericides,[2] or catalysts for esterification[3] or polymerization,[4] either by themselves or as derivatives.

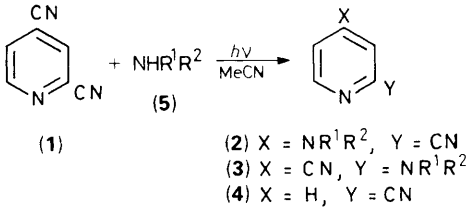
The synthesis of this class of compounds generally requires rather severe conditions, such as the reaction of ammonia or amines with halogenated heterocyclic derivatives at high temperature and pressure, or the classical Tschitschibabin reaction, which is not compatible with a number of substituent groups.[5] We have studied the photochemistry of substituted azaheteroaromatic bases for a number of years, and now report the results of a study of the photoinitiated reaction of primary and secondary amines with pyridines substituted with two cyano groups; one of the cyano groups is replaced by an amino group, and the other remains available for further conversion into other useful functional groups.

We reported earlier that, on irradiation, pyridine-2,4-dicarbonitrile (**1**) reacts *via* its triplet state with donors such as alkenes[6] or alcohols[7] in electron-transfer substitution reactions in which the product distribution is dependent on both solvent and pH. We thought that this mechanism may also apply to reactions of amines which have ionization potentials that are low enough to allow electron transfer to the heterocyclic base in its excited state. These predictions were found to be correct and the aim of this work is to establish the scope and the synthetic value of this reaction.

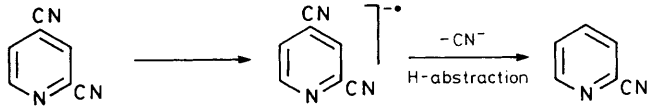
The products obtained on irradiation of various amines (**5**) in the presence of the dicarbonitrile (**1**) are in Scheme 1. Yields for the various products are reported in Table 1 and spectroscopic data and elemental analyses are in Table 2.

The structure of the amine plays an important role in determining the course of the reaction. For example with triethylamine and di-isopropylamine the only product isolated is pyridine-2-carbonitrile, while with 2,2,6,6-tetramethylpiperidine essentially no reaction occurs. In order to test the possibility that product formation may occur by a thermal reaction, a solution of (**1**) and diethylamine in acetonitrile was heated at the boiling point without irradiation. No reaction occurred indicating that product formation occurs *via* a photochemical process.

None of the amine substitution products isolated in this work had been reported previously, and so we needed additional evidence that our structure assignments were correct. We decided to determine unequivocally which cyano group is displaced in these reactions using the nuclear Overhauser effect (n.O.e.) for the two separated isomers (**2b**) and (**3b**) obtained from the reaction with isopropylamine. For the 2-amino substituted isomer (**3b**), an n.O.e. enhancement would be expected only for 3-H (δ 6.53) of the heterocyclic ring on irradiating the NH (δ 4.69) or C*H*$(CH_3)_2$ (δ 3.89) protons, and the converse would be true on irradiation at δ 6.53. For the other isomer (**2b**), irradiation of NH (δ 4.54) or C*H*$(CH_3)_2$ (δ 3.67) protons would enhance both 3-H and 5-H (δ 6.80 and 6.54 respectively). The strong n.O.e. enhancements that we observed are the ones expected for the assigned structures.



Scheme 1.



Scheme 2. $Ph_2C{=}O$, Pr^iOH, 350 nm, basic medium

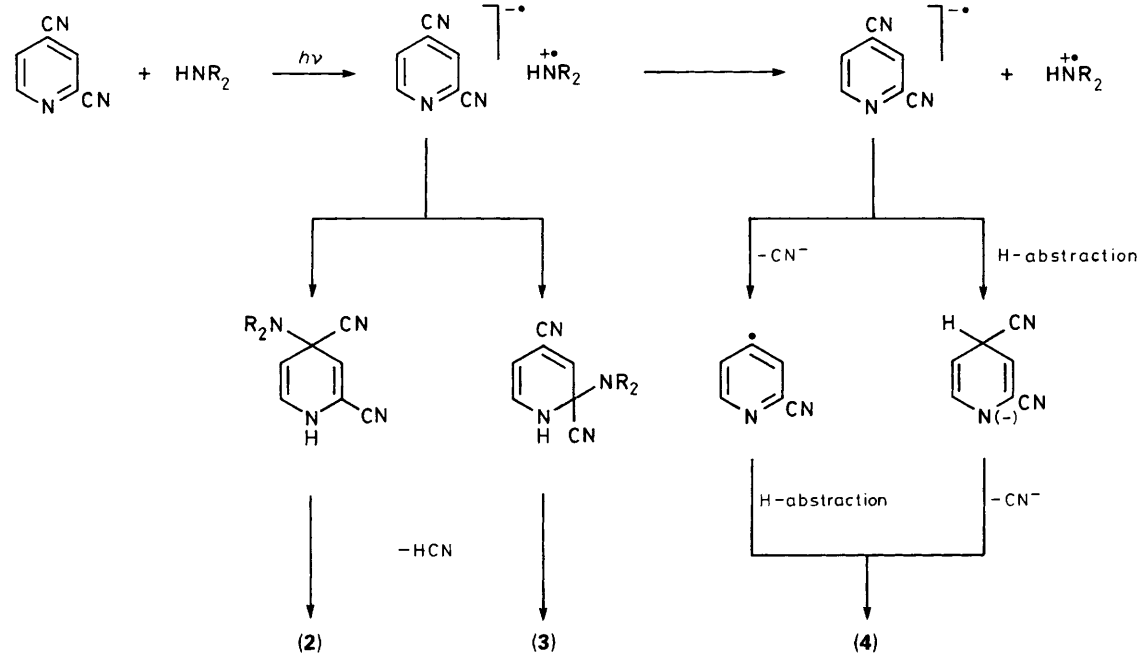
Since the ^1H n.m.r. chemical shifts for each class of derivatives appear to be characteristic (see Table 2), we could then assign the correct structures to all the other regioisomers without further problems. Although we do not know the mechanism of this reaction, we can speculate on the reactions involved in product formation on the basis of our previous work.[6,7] The mechanism by which substitution occurs must involve electron transfer from the amine to the excited heterocyclic base. The resulting radical anion can in principle undergo either elimination of the cyano group in the 4-position or protonation of the ring nitrogen. We found that in the reaction between (**1**) and propan-2-ol in the presence of benzophenone in basic medium (NaOH), fast decyanation occurs yielding pyridine-2-carbonitrile,[8] † (Scheme 2) although the primary process is probably different under these conditions. Assuming that in basic solution protonation does not occur, it may be concluded that in the reaction with amines also, the radical anion which is not protonated would undergo elimination. It follows then that the ratio between substitution and reduction should be related to the rates of the two competing processes: protonation and

† The reaction was carried out by irradiating a solution of (**1**) (1 mmol) and benzophenone (1 mmol) in propan-2-ol–water (4:1; 50 ml); pH adjusted to *ca.* 12 with NaOH) at 350 nm. Compound (**1**) was completely transformed into (**4**) in 1 h.

Table 1. Relative ratios of the aminoisomers, relative ratios between the aminoisomers and 2-cyanopyridine, yields of the aminoderivatives and total yields[a]

Amine	R^1	R^2	(2)/(3)	[(2) + (3)]/(4)	% Yield of (2) + (3)	Total % yield (2) + (3) + (4)
(5a)	Pr^n	H	0.58	0.27	10	46
(5b)	Pr^i	H	0.76	0.24	12	60
(5c)	Bu^t	H	0.63	0.62	14	37
(5d)	C_6H_{11}[b]	H	0.67	0.27	11	52
(5e)	Et	Et	1.36	0.53	26	76
(5f)	Pr^n	Pr^n	1.83	0.83	37	82
(5g)	$-[CH_2]_4-$		1.07	0.27	13	62
(5h)	$-[CH_2]_5-$		0.52	0.36	17	63
(5i)	$-[CH_2]_2O[CH_2]_2-$		0.82	1.38	20	34

[a] Pyridine-2,4-dicarbonitrile (1 mmol) and the amine (5 mmol) in MeCN (20 ml) and H_2O (5 ml), degased and then irradiated at 254 nm for 150 min. Values of the ratios were determined by gas chromatography and are ±0.05. Isolated yields are accurate to ±1%. [b] Cyclohexyl.



Scheme 3.

decyanation (Scheme 3). The data in Table 1 and results we have obtained with other reactions show that steric factors must play an important role in the electron-transfer process.

Since electron transfer may occur at relatively long distances[9] and need not be significantly affected by steric factors, a reasonable explanation for the steric effects observed in this study is that the electron transfer is preceded by the formation of an exciplex that is sensitive to the steric environment of the amine.

Furthermore, if we assume that substantial negative charge resides on the ring nitrogen of the radical anion of pyridine-2,4-dicarbonitrile, then the regioselectivity that we observe can be explained on the basis of attraction between the positive amine radical cation and the negatively charged ring nitrogen. This association is followed by a transfer of a proton from the amine to the ring nitrogen with simultaneous radical coupling between the amine nitrogen and the ring carbon at the 2-position. If the amine radical transfers a proton to the ring nitrogen but cannot couple simultaneously at the 2-position because of steric reasons then coupling may also occur at the 4-position, the position of highest spin density in the molecule.

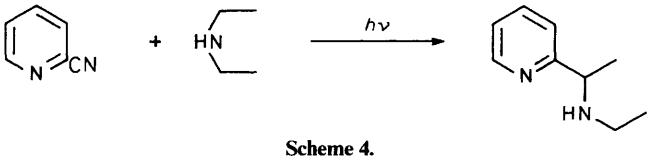
In this regard, all amines that contain $-NH_2$ or ring N–H groups except for (**5g**) react preferentially at the 2-position while amines in which the substituent groups cannot move out of the way such as (**5e**) and (**5f**) react preferentially at the 4-position rather than the 2-position.

A number of mechanistic paths could explain the formation of the reduction product (**4**). Since the highest spin density in the radical anion of (**1**) is expected at position 4, abstraction of hydrogen from the CH α to the amine group by the pyridyl radical anion could then occur at this position, and the intermediate could lose a cyanide ion and form (**4**). Conversely loss of the cyanide ion could precede hydrogen abstraction. It is also reasonable to assume that the new radical formed, the α-aminoalkyl radical, being a good reducing agent with an ionization potential of 5.4 eV,[10] similar to those of Li (5.39 eV) and Na (5.14 eV), could reduce either a pyridinyl radical or another molecule of (**1**) giving rise to a chain reaction. The effect of irradiation time on the ratio [(**2**) + (**3**)]:(**4**) was found not to vary in a predictable manner (see Table 3). Blank experiments showed that (**2**) and (**3**) are stable under our irradiation conditions, whereas pyridine-2-carbonitrile is not, and may react in a manner similar to that reported by Gilbert *et al.*[11] for pyridine and by us for pyridine-4-carbonitrile,[12] as shown in Scheme 4. This should lead to an increase of the ratio of (**2**) + (**3**) to (**4**) with time.

Table 2. Spectroscopic data and elemental analyses

Compound	M.p. (*t*/°C)	*m/z*	N.m.r. (δ)[a]	% Found (%Required) C	H	H
(2a) $C_9H_{11}N_3$	Oil	161, 143, 132, 103	8.22 (1H, d, H_A, J_{AB} 0.6), 6.85 (1H, d, H_C, J_{CB} 0.1), 6.59 (dd, H_B, J_{BA} 0.6, J_{BC} 0.1), 4.72 (1H, br s, NH), 3.15 (2H, q, CH_2N, $J_{1,2}$ 0.7), 1.69 (2H, m, CH_2CH_2Me, $J_{2,1}$ 0.7, $J_{2,3}$ 0.5), 1.01 (3H, t, Me $J_{3,2}$ 0.5)	67.3 (67.05)	7.0 (6.9)	25.9 (26.1)
(3a) $C_9H_{11}N_3$	Oil	161, 146, 132, 129, 119, 103	8.22 (1H, d, H_A), 7.72 (1H, dd, H_B), 6.61 (1H, d, H_C), 5.01 (1H, br s, NH), 3.28 (2H, q, CH_2N, $J_{1,2}$ 0.7), 1.65 (2H, m, CH_2 Me, $J_{2,1}$ 0.7 $J_{2,3}$ 0.5), 1.02 (3H, t, Me J 0.5)	66.9 (67.05)	6.9 (6.9)	26.3 (26.1)
(2b) $C_9H_{11}N_3$	Oil	161, 146, 142, 103	8.19 (1H, d, H_A), 6.80 (1H, d, H_C), 6.54 (1H, dd, H_B), 4.54 (1H, br s, NH), 3.67 (1H, m, CH, $J_{1,2}$ 0.6), 1.26 (6H, d, Me, $J_{2,1}$ 0.6)	66.9 (67.05)	6.9 (6.9)	26.3 (26.1)
(3b) $C_9H_{11}N_3$	55—56	161, 146, 103	8.18 (1H, d, H_A), 6.70 (1H, dd, H_B), 6.53 (1H, d, H_C), 4.69 (1H, br s, NH), 3.89 (1H, m, CH, $J_{1,2}$ 0.6), 1.25 (6H, d, Me, $J_{2,1}$ 0.6)	66.85 (67.05)	7.0 (6.9)	25.9 (26.1)
(2c) $C_{10}H_{13}N_3$	Oil	175, 161, 160, 120, 119, 103	8.21 (1H, d, H_A), 6.90 (1H, d, H_C), 6.67 (1H, dd, H_B), 5.52 (1H, br s, NH), 1.39 (9H, s, Me)	68.3 (68.5)	7.6 (7.5)	24.2 (24.0)
(3c) $C_{10}H_{13}N_3$	90—91	175, 160, 120, 119, 103	8.20 (1H, d, H_A), 6.68 (1H, dd, H_B), 6.55 (1H, d, H_C), 4.78 (1H, br s, NH), 1.41 (9H, s, Me)	68.4 (68.5)	7.55 (7.5)	24.2 (24.0)
(2d) $C_{12}H_{15}N_3$	115—116	201, 158, 144, 119, 103	8.20 (1H, d, H_A), 6.80 (1H, d, H_C), 6.54 (1H, dd, H_B), 4.52 (1H, br s, NH), 3.33 (1H, br s, CHN), 2.18—1.10 (10H, br s, $[CH_2]_5$)	71.5 (71.6)	7.34 (7.5)	21.1 (20.9)
(3d) $C_{12}H_{15}N_3$	86—87	201, 158, 144, 119, 103	8.22 (1H, d, H_A), 6.70 (1H, dd, H_B), 6.58 (1H, d, H_C), 4.80 (1H, br s, NH), 3.52 (1H, br s, CHN), 2.20—0.90 (10H, br s, $[CH_2]_5$)	71.8 (71.6)	7.4 (7.5)	20.7 (20.9)
(2e) $C_{10}H_{13}N_3$	77—78	175, 161, 160, 146, 103	8.22 (1H, d, H_A), 6.88 (1H, d, H_C), 6.60 (1H, dd, H_B), 3.40 (4H, q, CH_2), $J_{1,2}$ 0.7), 1.71 (6H, t, Me, $J_{2,1}$ 0.7)	68.7 (68.5)	7.3 (7.5)	23.8 (24.0)
(3e) $C_{10}H_{13}N_3$	56—57	175, 160, 146, 103	8.25 (1H, d, H_A), 6.66 (2H, s and d, H_B and H_C), 3.55 (4H, q, CH_2, $J_{1,2}$ 0.7), 1.20 (6H, t, Me, $J_{2,1}$ 0.7)	68.3 (68.5)	7.5 (7.5)	24.1 (24.0)
(2f) $C_{12}H_{17}N_3$	68—69	203, 174, 132, 103	8.18 (1H, d, H_A), 6.79 (1H, d, H_C), 6.52 (1H, dd, H_B), 3.25 (4H, t, CH_2N $J_{1,2}$ 0.8), 1.59 (4H, m, CH_2CH_2 Me, $J_{2,1}$ 0.8 and $J_{2,3}$ 0.6), 0.91 (6H, t, Me, $J_{2,1}$ 0.8)	71.05 (70.9)	8.3 (8.4)	20.5 (20.7)
(3f) $C_{12}H_{17}N_3$	43—44	203, 174, 139, 132, 112	8.21 (1H, d, H_A), 6.59 (2H, s and d, H_B and H_C), 3.40 (4H, m, CH_2N, $J_{1,2}$ 0.8), 1.55 (4H, m, CH_2CH_2Me, $J_{2,1}$ 0.8 and $J_{2,3}$ 0.6), 0.92 (6H, t, Me, $J_{3,2}$ 0.6)	71.1 (70.9)	8.2 (8.4)	20.75 (20.7)
(2g) $C_{10}H_{11}N_3$	119—120	173, 172, 144, 130, 103	8.23 (1H, d, H_A), 6.74 (1H, d, H_C), 6.50 (1H, dd, H_B), 3.33 (4H, m, CH_2N), 2.08 (4H, m, CH_2CH_2)	69.1 (69.3)	6.6 (6.4)	24.4 (24.3)
(3g) $C_{10}H_{11}N_3$	75—76	173, 145, 144, 103	8.28 (1H, d, H_A), 6.69 (1H, dd, H_B), 6.52 (1H, d, H_C), 3.50 (4H, m, CH_2N), 2.10 (4H, m, CH_2CH_2)	69.4 (69.3)	6.6 (6.4)	24.1 (24.3)
(2h) $C_{11}H_{13}N_3$	78—79	187, 186, 146, 131, 130, 103	8.25 (1H, d, H_A), 7.01 (1H, d, H_C), 6.71 (1 H, dd, H_B), 3.39 (4H, m, CH_2N), 1.69 (6H, m $[CH_2]_3$)	70.4 (70.6)	7.2 (7.0)	22.3 (22.4)
(3h) $C_{11}H_{13}N_3$	43—44	187, 158, 144, 132, 103	8.28 (1H, d, H_A), 6.80 (1H, d, H_C), 6.65 (1H, dd, H_B), 3.56 (4H, m, CH_2N), 1.69 (6H, m, $[CH_2]_3$)	70.4 (70.6)	6.9 (7.0)	22.6 (22.4)
(2i) $C_{10}H_{11}N_3O$	237—238	189, 131, 103	8.34 (1H, d, H_A), 7.06 (1H, d, H_C), 6.80 (1H, dd, H_B), 3.84 (4H, m, CH_2O), 3.49 (4H, m, CH_2N)	63.3 (63.5)	6.0 (5.9)	22.3 (22.21)
(3i) $C_{10}H_{11}N_3O$	140—141	189, 188, 158, 132, 103	8.30 (1H, d, H_A), 6.79 (2H, s and d, H_B and H_C), 3.75 (4H, m, CH_2O), 3.49 (4H, m, CH_2N)	63.6 (63.5)	5.6 (5.9)	22.2 (22.2)

[a] For solutions in $CDCl_3$. All coupling constants (J) are in Hz. H_A, H_B, and H_C refer respectively to the proton in position 6, 5 and 3 of the pyridine ring: J_{AB} and J_{BC} values are reported only for the first product; in all the other cases the values are the same. For the other J values, the numbers refer to the C atoms of the amine, starting from the one attached to nitrogen.



Scheme 4.

In our examples, in two of the four cases examined there are only slight changes in the ratios, while in the other two cases the changes in the ratios are significant but in one the ratio decreases and in the other it increases. Studies are now in progress to check these hypotheses and to extend this study to include aromatic amines and heteroaromatic bases with CN groups in different positions. Preliminary reactions seem promising.

Experimental

All the amines were freshly distilled before use. M.p.s are uncorrected. The solid products were crystallized from hexane–benzene. N.m.r. spectra were recorded on a Varian EM 390 90 MHz spectrometer and chemical shifts are reported in p.p.m. (δ) relative to Me_4Si as internal standard. Nuclear Overhauser effect (n.O.e.) spectra were recorded on Bruker CXP-300 spectrometer. n.O.e. difference spectra were obtained by subtracting alternatively off-resonance free-induction decays (f.i.d.s) from on-resonance induced f.i.d.s. n.O.e. values obtained have only a qualitative significance. For compound **(2b)** enhancements of 3- and 5-H were obtained irradiating NH

Table 3. Effect of the irradation time on the product distribution[a]

Amine	(2)/(3) 30 min	(2)/(3) 150 min	[(2) + (3)]/(4) 30 min	[(2) + (3)]/(4) 150 min
Pr^iNH_2 **(5b)**	0.72	0.76	0.25	0.24
Bu^tNH_2 **(5c)**	0.62	0.63	0.92	0.62
Et_2NH **(5e)**	1.33	1.36	0.43	0.53
$Pr^n{}_2NH$ **(5f)**	1.79	1.83	0.56	0.83

[a] Conditions as in Table 1, except for irradiation time variation. Ratios are accurate to +0.05.

(respectively 7 and 4%) or $(CH_3)_2CH$ (5 and 4%), while for compound (**3b**) the effect is only on 3-H (6 and 7%) on irradiating the same protons. Mass spectra were recorded with a Hitachi–Perkin-Elmer RMU 6D single focusing spectrometer. Gas chromatographic analyses were performed on a Dani 3800 gas chromatograph using a 2 m glass column (i.d. 2 mm) packed with 5% SP-1000 on 100/200 Supelcoport at 220 °C or a 2 m glass column (i.d. 2 mm) packed with 10% UCC-W 982 on chrom. W-AW-DMCS and temperature-programed from 120 to 235 °C (8 °C/min after the first 4 min) using a flame ionisation detector. A mixture of weighed compounds and standard was used to calibrate the detector response and peak areas were used to determine the product ratios.

All the photochemical reactions were run in quartz flasks in a RPR-100 Rayonet photochemical reactor. A mixture of (**1**) (1 mmol) and the appropriate amine (5 mmol) was dissolved in MeCN (20 ml) and water (5 ml), and the resulting solution was deaerated by bubbling N_2 for 20 min and irradiated at 254 nm for 30 or 150 min. The solvent was removed under reduced pressure and the residue was separated by standard flash chromatography[13] on Merck silica gel (0.040—0.063 mm) using hexane–ethyl acetate (2:1) [order of elution (**3**), (**1**), (**4**), (**2**)]; the residue was examined quantitatively by gas chromatography after addition of a known amount of an internal standard.

Spectral data are reported in Table 2.

Acknowledgements

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