NUCLEOPHILIC PHOTOSUBSTITUTION OF HALOGEN IN THE HETEROCYCLIC SERIES

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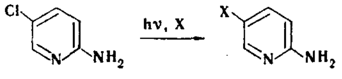
A new method is described for the introduction of a cyano group into pyridine and pyrimidine rings and for the introduction of nitro and thiocyano groups into the pyridine ring by UV irradiation of halo-substituted pyridines and pyrimidines in the presence of the appropriate nucleophiles.

In a synthetic respect, 2(5)-amino derivatives of pyridine and pyrimidine containing cyano or thiocyano groups in the 5(2) position are compounds that are relatively difficult to obtain. We have previously described [1, 2] the photosubstitution of halogen in the benzene ring by nitrite and cyanide ions. In order to accumulate experimental data and study the synthetic possibilities of photosubstitution in a number of heterocyclic compounds we investigated photosubstitution in the case of 2(5)-halo-5(2)-aminopyridines and pyrimidines.

Little data on the lability of halogen in the β position in aromatic compounds containing heteroatoms are available. The formation of 3-hydroxypyridine by irradiation of 3-bromopyridine in the presence of alkali is mentioned in [3]. Ultraviolet irradiation of bromopyridines in methanol in the presence of aliphatic amines leads primarily to dehalogenation [4].

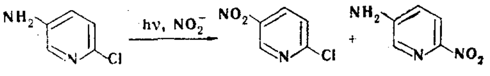
We have established that the halogen of 2-amino-5-chloropyridine (I) is replaced by nitro, cyano, and thiocyano groups during UV irradiation in the presence of nucleophiles.



I IIa-c

IIa X=NO$_2$; b X=CN; c X=SCN

2-Amino-5-thiocyanopyridine (IIc) was isolated from the photoreaction of 2-amino-5-chloropyridine with sodium thiocyanate. Inasmuch as the thiocyanate anion has ambident properties, both IIc and 2-amino-5-isothiocyanopyridine (III) can be formed in the reaction. The thiocyanation of 2-aminopyridine with copper thiocyanate was described in [5], and thiocyanopyridine structure IIc was assigned to the product. However, the properties of IIc differ from the characteristics of the product synthesized by thermal thiocyanation of 2-aminopyridine: a melting-point depression was observed for a mixture of the two substances, and the band of the stretching vibrations of the SCN group in the IR spectrum of IIc at 2195 cm^{-1} is shifted relative to the band of the compound obtained by the method in [5] (ν 2090 cm^{-1}). We note that the absorption of the SCN group in the IR spectrum of p-isothiocyanoaniline [6] is located at 2105 cm^{-1}, as compared with 2166 cm^{-1} for p-thiocyanoaniline [6]. Thiocyanopyridine IIc is apparently formed in the photoreaction, whereas aminoisothiocyanopyridine III was synthesized in [5].



IV V VI

Lensovet Leningrad Technologic Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1645-1648, December, 1974. Original article submitted January 23, 1974.

TABLE 1. Photosubstitution of Chlorine in Chloroaminopyridines and Pyrimidines by Various Nucleophilies (20-25°C)

Starting compound (concn., M)	Nucleophile (concn., M)	Solvent (water–tert-butyl alcohol) vol. %	Irradiation time, h	Conversion of starting compound, %	Reaction products, yields, % (with respect to substrate)
I (0,006—0,011)	$NaNO_2$ (0,186)	26	3	92	IIa 29
	KCN (0,130)	29	2	93	IIb, 76
	NaSCN (0,176)	29	3	100	IIc, 80
IV (0,0065—0,011)	$NaNO_2$ (0,193)	17	1,5*	98	V, 3,7 VI, 3,2
	KCN (0,13)	29	4	100	VII, 50
VIII (0,007)	KCN (0,13)	14	8	88	IX, 7
X	KCN (0,126)	30	12	100	XII, 87
XI	KCN (0,126)	15	4	100	XIII, 68

*With a DRL-400 lamp.

TABLE 2. Physicochemical Properties of the Photosubstitution Products

Compound	mp, °C (crystallization solvent)	Empirical formula	Found, %			Calc., %			IR spectrum (CN), cm^{-1}	UV spectrum in ethanol, λ_{max}, nm (log ε)
			C	H	N	C	H	N		
IIb	161—162 (benzene)	$C_6H_5N_3$	—	—	35,3	60,5	4,2	35,3	2206[a]	267 (4,36)
IIc	99—101 (benzene–hexane, 9 : 1)	$C_6H_5N_3S$[b]	47,4	3,6	27,9	47,7	3,3	27,8	2195 (SCN)[c]	257 (4,18) 304 (3,62)
VII	144—146 (benzene)	$C_6H_5N_3$	60,1	4,4	34,9	60,5	4,2	35,3	2212[a]	279 (4,32)
IX	269—271 (ethanol)	$C_7H_4N_4$	58,1	3,5	39,1	58,3	2,8	38,9	2270[c]	255 (3,87) 325 (3,64)
XII	122—124 (hexane)	$C_9H_{12}N_4$	61,6	7,1	32,1	61,4	6,8	31,8	2245[c]	269 (4,51)
XIII[d]	133—134 (hexane)	$C_7H_8N_4$	56,4	5,5	37,5	56,8	5,4	37,8	2260[c]	273 (4,49)

[a] In a thin layer.

[b] Found: S 21.3%. Calculated: S 21.2%.

[c] In KBr pellets.

[d] PMR spectrum: 3.16 (6H), singlet, dimethylamino group; 8.4 (2H), singlet, aromatic proton.

The UV-induced substitution of chlorine by nitro and cyano groups occurs in the reaction of 2-chloro-5-aminopyridine (IV) with nitrite and cyanide ions. The formation of 2-fluoro-5-nitropyridine (V) was also established in the presence of sodium nitrite.

The replacement of an amino group by a nitro group in the benzene series has been described [7]. The reaction apparently proceeds through a step involving a diazo compound*, the formation of which may be due to diazotization of the excited state of the arylamine by the nitrite ion [7] or of the arylamine in the ground state by the NO_2 radical. The latter is formed during the photoexcitation of the nitrite ion [8].

In the case of 3,5-dichloro-4-aminopyridine (VIII) it was found that dichloroaminopyridines, like dichloroanilines [2], exchange both chlorine atoms for a cyano group: 3,5-dicyano-4-aminopyridine (IX) is detected in the reaction products.

2-(n-Butylamino)-5-bromo- and 2-(N,N-dimethylamino)-5-bromopyridines (X and XI) were also subjected to the reaction, and the corresponding cyano derivatives (XII and XIII, Tables 1 and 2) were obtained.

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*The previously described "photodenitration" [9] of halonitrobenzenes in the $NaNO_2$–aqueous methanol system is probably associated with photoreduction of the nitro group to an amino group [1] by diazotization of it under photolysis conditions and replacement of the diazo group by hydrogen ("photodenitration") or the nitro group [7]. Thus the photolysis of p-anisidine under the conditions in [9] gives (according to gas–liquid chromatography [1]) 6% p-nitroanisole and 3% anisole (60% conversion of the starting compound).

EXPERIMENTAL

The IR spectra of KBr pellets or thin layers of the compounds were recorded with IKS-22 or UR-10 spectrometers. The UV spectra of ethanol solutions were recorded with an SFD-2 spectrophotometer; solution concentrations of $1.82\text{-}4.2 \cdot 10^{-5}$ M were used to determine the extinctions of IIb, c, VII, XII and XIII, whereas solution concentrations of $8.34\text{-}9.74 \cdot 10^{-5}$ M were used for IX. The PMR spectrum of cyanopyrimidine XIII was obtained from a 10% solution in $CDCl_3$ at room temperature with an R-12 spectrometer (Perkin–Elmer, 60 MHz) with hexamethyldisiloxane as the internal standard.

The irradiation was carried out in a 350-400 ml reactor with the full spectrum of a PRK-4 immersible mercury lamp (250 W) through a water-cooled quartz condenser; the solution was stirred by means of nitrogen or argon. The workup of the reaction solutions and the isolation of the reaction products were accomplished by the same method in all cases: after the irradiation, three-fourths to two-thirds of the volume of tert-butyl alcohol was removed by distillation, the residue was extracted with ether, the ether was dried and removed by distillation, and the residual alcohol was air evaporated. The course of the reaction was monitored by thin-layer chromatography (TLC) and from the UV spectra. The mixture of products was separated by preparative TLC on aluminum oxide. In the experiments with KCN, in order to avoid hydrolysis of the final product, the alcohol was removed by vacuum distillation at a bath temperature of no more than 50°. The reaction conditions are presented in Table 1, and the properties of some of the compounds are presented in Table 2.

After irradiation and the usual workup, 0.12 g of precipitate was isolated from 0.3 g of 2-amino-5-chloropyridine (I) [10] and 5 g of $NaNO_2$. Treatment of this precipitate with 15 ml of ether yielded 0.07 g of 2-amino-5-nitropyridine (IIa) with mp 188-190° (from water) (mp 188° [11]). According to preparative TLC [Al_2O_3, chloroform–ethanol (8 : 2)], the ether extract contained 0.025 g of I and 0.023 g of IIa, which were identified by TLC and from the UV spectra with authentic samples.

Irradiation of 0.5 g of I and 3 g of KCN gave 0.38 g of a precipitate containing, according to preparative TLC [Al_2O_3, petroleum ether (bp 40-70°)–ethanol (8 : 2)] and the UV spectrum, 0.027 g of starting I. The precipitate was crystallized twice from benzene with activated charcoal (Table 2). According to [12], cyanopyridine IIb has mp 163-164°.

Irradiation of 0.5 g of pyridine I and 5 g of NaSCN gave 0.47 g of crude thiocyanopyridine IIc, which, according to TLC (Al_2O_3, ether), did not contain the starting compound. The irradiation was interrupted every 30 min in order to remove film from the condenser. Product IIc was recrystallized twice from benzene with activated charcoal (Table 2).

A 0.5-g sample of pyridine IV [13] and 8 g of sodium nitrite in 600 ml of 17% aqueous tert-butyl alcohol were irradiated with a DRL-400 mercury lamp (400 W). The alcohol was removed by distillation, and the solution was extracted with ethyl acetate. The residue remaining after removal of the ethyl acetate by distillation was passed through a column filled with Al_2O_3 with successive elution with 1) ether–hexane (1 : 1), 2) ether, and 3) petroleum ether (bp 40-70°)–ethanol (8 : 2). The following products were isolated (from five experiments): 1) 0.105 g of 2-chloro-5-nitropyridine (V) with mp 105-107° (from water) (mp 108° [13]; no melting-point depression was observed), 2) 0.05 g of 2-chloro-5-aminopyridine (IV), identified by TLC with an authentic sample, and 3) 0.1 g of 2-nitro-5-aminopyridine (VI) with mp 233-234° (from water) (mp 234° [14]).

Irradiation of 0.5 g of 2-chloro-5-aminopyridine (IV) and 3 g of KCN gave 0.22 g of 2-cyano-5-aminopyridine VII. The product was crystallized from benzene with activated charcoal three times (Table 2).

The photoreaction of 3,5-dichloro-4-aminopyridine (VIII) [15] (0.4 g) and KCN (3 g) was repeated four times. The solution was extracted with ether without removal of the alcohol by distillation. The usual workup gave 1 g of a mixture of substances, from which 0.35 g of the starting compound, identified by TLC and a mixed-melting-point determination, and 0.1 g of 3,5-dicyano-4-aminopyridine (IX) (Table 2), were isolated by preparative TLC (Al_2O_3, ether). The two compounds are probably products of complete and partial hydrolysis of dicyano derivative IX, which was not identified.

The reaction of 0.3 g of 2-(n-butylamino)-5-bromopyrimidine (X) [16] and 3 g of KCN gave, after removal of the alcohol by distillation, 0.07 g of a precipitate; an additional amount (0.13 g) was extracted from the filtrate with ether. 2-(n-Butylamino)-5-cyanopyrimidine (XII) was crystallized twice from hexane with activated charcoal (Table 2). After irradiation, 0.2 g of 2-(N,N-dimethylamino)-5-cyanopyrimidine XIII (Table 2) was obtained from 0.4 g of 2-(N,N-dimethylamino)-5-bromopyrimidine XI [4] and 3 g of KCN by extraction with ether (without removal of the alcohol by distillation).

LITERATURE CITED

1. A. V. El'tsov, O. V. Kul'bitskaya, and A. N. Frolov, Zh. Organ. Khim., 8, 76 (1972).
2. O. V. Kul'bitskaya, A. N. Frolov, and A. V. El'tsov, Zh. Organ. Khim., 9, 2316 (1973).
3. E. Havinga and M. Kronenberg, Pure Appl. Chem., 16, 173 (1968).
4. J. Nasielski, A. Kirsch-Demesmaeker, and R. Nasielski-Hinkens, Tetrahedron, 28, 3767 (1972).
5. J. Kolmer, H. Brown, and G. Raiziss, J. Pharm. Exp. Therap., 61, 253 (1937).
6. L. Bellamy, New Data on the IR Spectra of Complex Molecules [Russian translation], Mir, Moscow (1971), p. 65.
7. A. V. El'tsov, A. N. Frolov, E. V. Smirnov, and É. M. Sof'ina, Zh. Organ. Khim., 8, 1334 (1972).
8. P. Ayscough and R. Collins, J. Phys. Chem., 70, 3128 (1966).
9. A. N. Frolov and A. V. El'tsov, Zh. Organ. Khim., 6, 637 (1970).
10. A. E. Chichibabin and A. F. Egorov, Zh. Russk. Fiz.-Khim. Obshchestva, 60, 686 (1928).
11. A. E. Chichibabin (Tschitschibabin) and A. V. Kirsanov (Kirsanow), Ber., 61, 1228 (1928).
12. C. Räth and G. Prange, Ann., 467, 4 (1928).
13. Yu. M. Yurtilova and I. A. Svertilova, Methods for the Synthesis of Chemical Preparations [in Russian], Vol. 20, Moscow (1969).
14. H. den Hertog, and C. Jouwersma, Rec. Trav. Chim., 72, 125 (1953).
15. H. den Hertog, J. Schodt, J. de Bruyn, and A. de Klere, Rec. Trav. Chim., 69, 692 (1950).
16. D. Brown and R. Foster, Austral. J. Chem., 19, 2321 (1966).