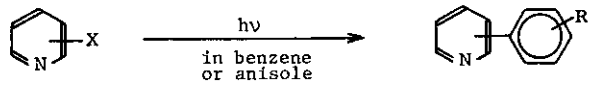
PHOTO-ARYLATION. II.[1] PHOTO-REACTION OF HALOPYRIDINES WITH BENZENE

Masanao Terashima*, Kohichi Seki, and Chihiro Yoshida
Faculty of Pharmaceutical Sciences, Higashi Nippon Gakuen University
Ishikari-Tobetsu, Hokkaido 061-02, Japan
Yuichi Kanaoka
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

Abstract-Photolysis of halopyridines in benzene afforded corresponding phenylpyridines. The reactivities of halopyridines in the reactions increased in the order of Cl < Br ≃ I. They were also dependent on the position of halogen on the ring, thus, the order of 2 > 3 > 4 for bromo- and iodopyridines, 3 > 2 > 4 for chloropyridines were observed. Effects of bases and solvents on the reaction were investigated. Homolytic mechanism of the present reaction would be suggested by the photolysis of halopyridines in anisole.

While several groups of workers recently demonstrated that photolysis of halobenzenes in aromatic solvents provided a synthetically useful method for substituted biphenyls,[2] few applications of the method to syntheses of arylheterocycles have been reported.[3] In the present paper, we describe the photo-reaction of halopyridines (1) with benzene and anisole as a prior study for a general synthetic method of heterocyclic compounds via intermolecular photo-arylation.



1 X=Cl, Br, I

2 R=H, CH_3O

a, 2- ; b, 3- ; c, 4-

A solution of halopyridines (1, 3 mmol) in benzene (300 ml) was irradiated with a 60-W low-pressure mercury lamp for 2 h and the results were listed in Table I. Photo-products, phenylpyridines (2, R=H), were isolated by column chromatography (silica gel / CH_2Cl_2), and characterized by their spectra (MS, nmr) and mp.

Table I. Yield of phenylpyridines (2, R=H) (%)[a,b]

halo-pyridine	Cl	Br	I
2-	4 (93)	40 (48)	49 [46] (51)
3-	9 (86)	16 (80)	30 [29] (50)
4-	1 (98)	10 (88)	4 [4] (96)

a) Yield determined by GLC.†; [ ], isolated yield. ( ), recovery of starting material by GLC.
b) ref. 4.

It can be seen from Table I, although some unreliabilities caused mainly by precipitation of hydrohalides of both starting materials and products remain, that the reactivities of halopyridines in the reactions increased in the order of Cl < Br ≈ I. In addition, the reactivities also vary with the position of halogen on pyridine ring. Thus, in iodo- and bromopyridine series, reactivities decreased in the order of 2 > 3 > 4, while in the case of chloropyridines 3 > 2 > 4 was observed. To prevent the salt-formation of pyridine bases proceeded concomitantly during the reaction, it was carried out with 1a-Br in the presence of bases and the results were summerized in Table II.

Table II. Effect of bases on the photolysis of 1a-Br in benzene[a]

base	equiv. mol	Yield[b] 2a (R=H)	recovered 1a-Br
----	-----	40	48
t-$BuNH_2$	1.0	72	19
	3.0	62	20
Et_3N	1.0	49	47
K_2CO_3	4.5	41	39

a) 1a-Br (3 mmol), benzene (300 ml), 2 h.
b) Yield determined by GLC.†

Distinct accelerating effect with t-butylamine was observed from Table II. Thus, photolysis of 1a-Br in benzene with t-butylamine (3.0 equiv. mol.) for 6 h in the same conditions described above gave 2-phenylpyridine (2a, R=H) in 75 % isolated yield.

From the synthetic view point, it would be desirable to carry out the reaction in an appropriate solvent. Therefore, influence of solvents on the reaction was examined with 1a,b and the results

were summerized in Table III.

Table III. Syntheses of phenylpyridines (2a,b, R=H) in various solvents[a)]

pyridine	Yield (%)[b)] hexane	CH_2Cl_2	t-BuOH
2-Cl	1 (82)	3 (73)	3 (73)
3-Cl	1 (87)	4 (77)	9 (65)
2-Br	18 (80)	16 (48)	10 (47)
3-Br	10[c)] (76)	8 (53)	10 (51)
2-I	5[c)] (60)	30 (56)	19 (45)
3-I	0[c)] (59)	46 (51)	8 (71)

a) Halopyridine (1 mmol) and benzene (10 ml) were irradiated for 2 h in each solvent (90 ml).
b) Yield determined by GLC.†; ( ), recovery of starting material by GLC.
c) The main product was pyridine.

n-Hexane would be an adoptable solvent for the reactions of bromopyridines in view of the good recovery of starting materials, while those of iodopyridines in it afforded pyridine as a major product, indicating typical radical processes of the reactions. In the case of iodopyridines, CH_2Cl_2 may be used as a solvent in which the reactions seemed to be accelerated.[3c] Reactions in t-BuOH were accompanied by significant side reactions which we didn't investigate further.

As to the reaction mechanism of the arylation by photolysis of halobenzenes, it has been generally recognized that the reactions proceed by a radical mechanism.[2] We investigated the photolysis of halopyridines in anisole to obtain some aspects related to the reaction mechanism in a similar manner to the work of Robinson and Vernon.[2c] 2- or 3-Halopyridines (5 mmol) in anisole (100 ml) were irradiated for 6 h as described for the reactions in benzene. After usual work-up, isomer distribution ratios of the products (2a,b; R=CH_3O) were determined by GLC analysis† (Table IV).

Table IV. Isomer distribution of methoxyphenylpyridines in the photolysis of 2- or 3-halopyridines in anisole (%)

halo-pyridine	2-(methoxyphenyl)pyridine o[a)]	m[b)]	p[c)]	3-(methoxyphenyl)pyridine o[a)]	m[d)]	p[e)]
Cl	59	20	21	61	16	23
Br	53	16	31	69	13	18
I	52	13	35	76	8	16

a) ref. 4.
b) mp (picrate) 158.5-159.5°C.
c) ref. 5.
d) obtained as a mixture of ortho / meta isomers characterized by GC-MS and nmr.
e) ref. 6.

The mixture of methoxyphenylpyridines obtained was also purified by column chromatography [silica gel pre-treated with AcOH / acetone:benzene = 10:1 (for 2-isomer series) or with HCO_2H / acetone: hexane = 10:1 (for 3-isomer series)], and isomers were characterized by their spectra (MS, nmr),[7,8] mp and elemental analyses. These results were nearly comparable to those found for halobenzenes by Robinson and Vernon,[2c] and would suggest a homolytic mechanism for the photolysis of halopyridines. The decrease of ortho/para ratios of the products observed particularly with 1a-Br and 1a-I in the 2-isomer series was not the result of o,p-isomerization reported for 2-phenylthiophene[9] or for o-methylbiphenyl,[10] because no rearrangement was observed on irradiation of 2-(o-methoxyphenyl)pyridine in the same conditions employed above. Effects of the neighboring ring-nitrogen to the reaction mechanism might be taken in consideration for 1a-Br and 1a-I in the 2-isomer series.[11]
Further studies for the application of the present reaction to syntheses of heterocycles are now in progress.

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† GLC analyses were performed by following conditions; column size, 1.5m x 3 mm; column packing, 1.5 % SE-30 on Chromosorb W (60-80 mesh); column temp., 80-200°C (program rate: 4°C/min); flow rate (N_2), 30 ml/min; internal reference, naphthalene or 3-bromopyridine (in the case of iodopyridine).

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