PHOTO-ARYLATION III[1]: SYNTHESIS OF 2-HETEROARYLPYRIDINES

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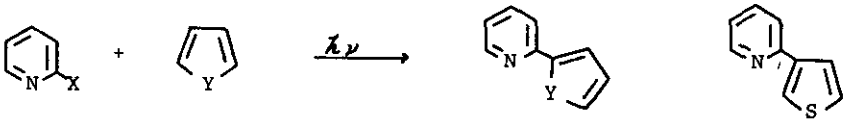
Abstract——The title compounds were prepared in satisfactory yields by photo-reaction of 2-halopyridine (halogen; I, Br) with five membered heteroaromatics.

In the course of our studies on the photo-reaction of halopyridines, it was found that 2-iodopyridine behaves like an electrophile in the reaction with substituted benzenes[2], suggesting that the formation of 2-arylpyridines would be efficiently improved by the use of electron-rich substrates. Although there are some reports on the synthesis of 2-heteroarylpyridines[3-10], these methods were generally limited to particular compounds and gave low yields. On the other hand, the synthesis of 3-heteroarylpyridines has been successfully achieved by using the modified Gomberg reaction[10] or by photolysis of 3-iodopyridine[11]. In the present paper, we wish to describe a facile synthesis of 2-heteroarylpyridines by the photo-reaction of 2-halopyridine (halogen; I, Br) with five membered heteroaromatics.

A solution of 2-iodopyridine (**1a**) (3 mmol) and a heterocyclic compound (**2a**-**d**) (30 mmol) in dichloromethane (300 ml)[1a] in the presence of aq. K_2CO_3 (60 mmol/30 ml) was irradiated with a 60 W low pressure mercury lamp for 10 h at room temperature to afford the corresponding 2-heteroarylpyridine (**3a**-**d**). The results are summarized in Table I.

With **2a**-**c**, 2-pyridinylation took place exclusively at the 2 position giving **3a**-**c** as a single isomeric product. In contrast, the reaction proceeded less regio-selectively with **2d** affording isomeric **3d** and **3e** in the ratio of 80:20. Irradiation of **3d** under the same conditions as used in the present reaction ruled out the possibility of photo-isomerization of **3d** to **3e**[8].



1a (X=I)
1b (X=Br)

2a, Y=O
b, NH
c, NCH_3
d, S

3a, Y=O
b, NH
c, NCH_3
d, S

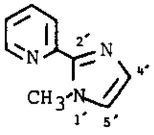
3e

Table I. 2-Pyridinylation of Heterocycles

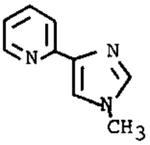
1	2	3	mp (°C)	yield (%)*	recovered 1 (%)
a	a	a	165-6(picrate)[3,4,5]	42	31
b	a		(from ethanol)	32	55
a	b	b	87-7.5[6,7]	32	38
b	b		(from hexane)	41	73
a	c	c	140-41(picrate)[12]	28	41
b	c		(from ethanol)	29	55
a	d	d	61-1.5[4,8,9]	49	36
		+	(from petr. ether)		
b	d	e	oil[8]	38	53

*; Given by GLC, based on 1 consumed.

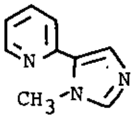
The observed regioselectivity of 1a toward 2 was in accord with those obtained in 3-pyridinylations[10,11] and 5-pyrimidinylation of 2[13].
Irradiation of a solution of 1a and 1-methylimidazole in dichloromethane afforded 4 (R=CH_3) as a mixture of three regio-isomers (4a-c) in the ratio of 18:24:58 (combined yield, 16.5%) together with recovered 1a (20% yield). The physical data of these compounds are listed in Table II.



4a



4b



4c

Table II. Physical Data for 4a, 4b and 4c

Compd.[a,b)]	MS(m/e)(%)	^{1}H-NMR($CDCl_3$) (J(Hz))[c)]							
		H-3	H-4	H-5	H-6	H-2'	H-4'	H-5'	CH_3
4a	159(M^+, 47)	8.10	7.66	7.14	8.49	--	6.91/7.06	7.06/6.91	4.08
	158(100)	(8.5^{d})	(8.5^{t})	$(8.5,5^{dd})$	(5^{d})		(s)	(s)	(s)
4b	159(M^+,100)	7.88	7.61	7.04	8.45	7.39/7.49	--	7.49/7.39	3.67
		$(8.^{d})$	(8^{t})	$(8,5^{dd})$	(5^{d})	(s)		(s)	(s)
4c	159(M^+, 63)	7.57	7.61	7.06	8.51	7.42/7.35	7.35/7.42	--	3.95
	158(100)	(7.5^{d})	(7.5^{t})	$(7.5,5^{dd})$	(5^{d})	(s)	(s)		(s)

a) mp(°C)(uncorr.): 4a(picrate), 184-186; 4b, 127.5-128.5; 4c(picrate), 170-172.

b) Satisfactory analytical data were obtained.

c) Abbreviations: s, singlet; d, doublet; t, triplet.

The photo-reaction of 1a with imidazole, however, gave many spots on thin layer chromatography and the isolation of the intended coupled products (4, R=H) failed. The present 2-pyridinylation of 2 was also conducted in the similar manner as described above using 2-bromopyridine (1b) in hexane as a solvent and furnished the corresponding 3 in considerable yields as shown in Table I. These results indicate that the bromo derivative is also successfully available for the photo-chemical synthesis of varying arylpyridines.

Further studies on the mechanistic features and the utility of the bromide (1b) in the present reaction are in progress.

REFERENCES AND NOTES

1. Photo-arylation II; M. Terashima, K. Seki, C. Yoshida and Y. Kanaoka, *Heterocycles*, 1981, **15**, 1075. A part of this work was presented at the Symposium on Photochemistry 1981, Sep. 1981, Sapporo, Japan.
2. M. Terashima, K. Seki, C. Yoshida and Y. Kanaoka, Abstract Papers, the 101 st Annual Meeting of the Pharmaceutical Society of Japan, Kumamoto, Apr. 1981, p. 374.
3. P. Ribereau, G. Nevers, G. Queguiner and P. Pastour, *C. R. Acad. Sci.*, Ser. C, 1975, **280**, 293.
4. Ch. Jutz, R. M. Wagner, A. Kraatz and H. G. Loebering, *Justus Libigs Ann. Chem.*, **1975**, 874.
5. J. F. Bunnet and P. Singh, *J, Org. Chem.*, 1981, **46**, 4567.
6. J. Firl, *Chem. Ber.*, 1968, **101**, 218.
7. Th. Severin, P. Adhikary and I. Schnabel, *Chem. Ber.*, 1969, **102**, 1325.
8. H. Wynberg, T. J. van Bergen and R. M. Kellogg, *J. Org. Chem.*, 1969, **34**, 3175.
9. M. Kumada, K. Tamao and K. Sumitani, *Org. Synth.*, 1978, **58**, 127.
10. G. Vernin and J. Metzger, *J. Org. Chem.*, 1975, **40**, 3183.
11. H. Ryang and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, **1972**, 594.
12. R. A. Heckman and F. W. Best, *Tobacco. Int.*, 1981, **183**, 83.
13. D. W. Allen, D.J. Buckland, B. G. Hutley, A. C. Oades and J. B. Turner, *J. Chem. Soc., Perkin Trans. 1*, **1977**, 621.

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