PHOTOREACTION OF 4-IODOPYRIDINE WITH HETEROAROMATICS[1]

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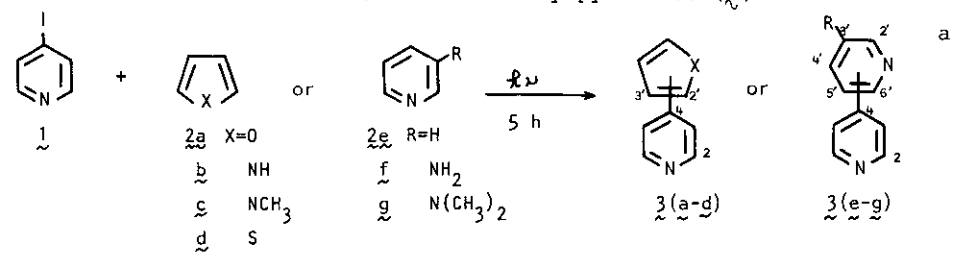
Abstract———Photoreaction of 4-iodopyridine with various heteroaromatics leads to give the corresponding 4-heteroarylpyridines in appreciable yields.

Heteroarylpyridines have been of interest in view of the various biological activities.[2] Although some useful procedures for the synthesis of 2- and 3-arylpyridines have been reported,[3] the synthetic methods of 4-arylpyridines are few[2a,4] and their preparation is generally difficult. Recently, Saeki et al. reported the synthesis of 4-arylpyridines by using the modified Gomberg reaction of 4-aminopyridine N-oxide,[5] while Terashima et al. successfully prepared 4-arylpyridines from diethyl(4-pyridyl)borane.[6] Very recently, the available photochemical synthesis of 4-arylpyridines has been attained by Tsuchiya et al. by the reaction of azabenzoyloxime derivatives with aromatic substrates.[7] In the course of our studies on the photolysis of halopyridines, we previously found that the photoreaction of 4-iodopyridine with benzenes afforded the corresponding 4-arylpyridines in appreciable yields.[8] In this paper, we wish to describe the further application of the reaction to heteroaromatic compounds.

A solution of 4-iodopyridine (1)[9] (1 mmol) and a heteroaromatic compound (2)(10 mmol) in dichloromethane (100 ml) was irradiated with a 60 W low pressure mercury lamp for 5 h under atmospheric pressure of argon at room temperature to afford the corresponding 4-heteroarylpyridine (3), and the results are summarized in the Table.

With five-membered heteroaromatic compounds, the reaction proceeded regioselec-

Table 1. 4-Heteroarylpyridines (3)



2	Reaction solvent	Heteroarylpyridine (3)			
No.		No.	Site	Yield(%)[b]	mp(°C)
2a	CH_2Cl_2	3a	2'	34	65- 66 (lit. 69)[2a]
2b	"	3b	2'	56	170-172 (lit. 175)[10]
2c	"	3c	2'	69	63- 63.5
2d	"	$3d_2$'	2'	29	93- 93.5 (lit. 92-92.5)[11]
		$3d_3$'	3'		138-138.5 (lit. 138.5-139)[11]
2e	"	3e	--[c]	4[12]	
	CH_3CN		--[c]	6	
2f	CH_2Cl_2		--[c]	17	
	CH_3CN	$3f_2$'	2'	41[d]	146-149
		$3f_4$'	4'		166-168 (lit. 170-172)[13]
2g	"	$3g_2$'	2'		146-147 (dipicrate)
		$3g_4$'	4'	45[d]	228-231 (dipicrate)
		$3g_6$'	6'		193-194

a: Numbering demonstrated in the scheme is used in this paper. b; The yields were determined by GLC on the bases of 4-iodopyridine consumed. c; Isomer ratio was not determined. d; The yields and the isomer ratio were given by isolation ($3f_2$':$3f_4$'=84:16, $3g_2$':$3g_4$':$3g_6$'=51:20:29).

tively to afford the corresponding 4-(2-heteroaryl)pyridines (3a-3c) as single products, with an exception of the reaction with thiophene (2d) which was accompanied with the formation of a small amount of regioisomer 4-(3-thienyl)pyridine ($3d_3$')($3d_2$':$3d_3$' = 87:13 on GLC). The reaction with six-membered N-heterocycles, i.e., pyridine (2e) and pyrazine in dichloromethane, was significantly retarded and scarcely gave the coupling products (not detectable for pyrazine).

The reaction with pyridine in acetonitrile solution also resulted in low yield. However, it was found that this difficulty could be circumvented by introducing an amino group into the pyridine ring.

Thus, the reaction of 1 with 3-aminopyridine (2f) in acetonitrile instead of dichloromethane afforded 4-(3-amino-2-pyridyl)pyridine (3f$_2$,) as a major product. Similarly, the reaction with 3-(N,N-dimethyl)aminopyridine (2g) afforded the corresponding dimethylamino derivatives (3g) in similar yields, though less regioselectively. In view of the report on the electron-transfer mechanism in the photoreaction of iodobenzene with dimethylaniline, these results might be recognized as the participation of an electron transfer from aminopyridine to 1, generating the pyridyl radical efficiently.[14] The reaction of 1 with 3-acetaminopyridine, however, resulted in deacetylation to give appreciable amounts of 3-aminopyridine as a sole isolable product. The structural assignments of new compounds obtained by the reaction were essentially made on the basis of elemental analyses, mass spectra, and ^{1}H-NMR spectra.

Because of a simple procedure and appreciable yields, the present method may provide a facile synthesis of 4-hetroarylpyridines.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H-NMR spectra were measured in a solution of $CDCl_3$ with TMS as an internal standard on a JEOL FX-90Q spectrometer (90 MHz). MS were determined on a Shimadzu LKB-9000 GC-mass spectrometer. Gas liquid chromatography (GLC) (2% Fluoxylate-K)' was carried out with a Shimadzu GC-7A gas chromatograph equipped with a hydrogen flame-ionization detector.

General procedure

A solution of 4-iodopyridine (1 mmol) and a substrate (10 mmol) in dichloromethane (100 ml) was irradiated with a 60 W low pressure mercury lamp (Eiko-sha) for 5 h under atmospheric pressure of argon at room temperature. The reaction mixture was extracted with 10% hydrochloric acid. The aqueous layer was neutralized with K_2CO_3 and extracted with dichloromethane. After concentration of the dried (Na_2SO_4) dichloromethane solution in vacuo, the residual oil was chromatographed on silica

gel (Merck Lobar column, LiChroprep Si 60) or on aluminum oxide F254 (type E) pre-coated TLC plates (Merck)(as for the reaction with 3-aminopyridine (2f)) to afford the corresponding 4-heteroarylpyridine. Following solvent systems were used as eluents: CH_2Cl_2-ether = 5:1 for 3a and 3c, AcOEt-CH_2Cl_2 = 5:1 for 3b, ether-hexane = 5:1 for 3d, ether for 3f, and hexane-AcOEt-Et_3N = 20:1:1 for 3g.

4-(1-Methylpyrrol-2-yl)pyridine (3c)

^{1}H-NMR: δ 8.58(2H, d, J = 4.5 Hz, 2- and 6-H), 7.30(2H, d, J = 4.5 Hz, 3- and 5-H) 6.78(1H, dd, J = 2, 3 Hz, 5'-H), 6.42(1H, dd, J = 3.5, 2 Hz, 3'-H), 6.22 (1H, dd, J = 3.5, 3 Hz, 4'-H), 3.75(3H, s, $-NCH_3$). MS m/z: 158(M^+, 100). Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 76.24; H, 6.36; N, 17.71.

4-(3-Amino-2-pyridyl)pyridine (3f$_2$')

^{1}H-NMR: δ 8.71(2H, d, J = 5 Hz, 2- and 6-H), 8.16(1H, dd, J = 4, 2 Hz, 6'-H), 7.65(2H, d, J = 5 Hz, 3- and 5-H), 7.11(1H, d, J = 4 Hz, 5'-H), 7.10(1H, d, J = 2 Hz, 4'-H), 3.8-4.1(2H, $-NH_2$). MS m/z: 171(M^+, 100), 170(82). Anal. Calcd. for $C_{10}H_9N_3$: C, 70.15; H, 5.30; N, 24.55. Found: C, 70.23; H, 5.26; N,24.79.

4-(3-Amino-4-pyridyl)pyridine (3f$_4$')

^{1}H-NMR: δ 8.74(2H, d, J = 5 Hz, 2- and 6-H), 8.19(1H, s, 2'-H), 8.10(1H, d, J = 5 Hz, 6'-H), 7.42(2H, d, J = 5 Hz, 3- and 5-H), 7.02(1H, d, J = 5 Hz, 5'-H), 3.7-3.9(2H, $-NH_2$). MS m/z: 171(M^+, 100), 170(32). High-resolution MS m/z: Calcd. for $C_{10}H_9N_3$ 171.0808; Found 171.0809.

4-(3-Dimethylamino-2-pyridyl)pyridine (4g$_2$')

^{1}H-NMR: δ 8.67(2H, d, J = 5 Hz, 2- and 6-H), 8.30(1H, dd, J = 4.5, 2 Hz, 6'-H), 7.85(2H, d, J = 5 Hz, 3- and 5-H), 7.38(1H, dd, J = 8.5, 2 Hz, 4'-H), 7.20(1H, dd, J = 8.5, 4.5 Hz, 5'-H), 2.63(6H, s, $-N(CH_3)_2$). MS m/z: 199(M^+, 100), 198(38). Anal. Calcd. for $C_{24}H_{19}N_9O_{14}$ (dipicrate): C, 43.84; H, 2.91; N, 19.18. Found: C, 43.87; H, 2.87; N, 18.96.

4-(3-Dimethylamino-4-pyridyl)pyridine (4g$_4$')

^{1}H-NMR: δ 8.69(2H, d, J = 5.5 Hz, 2- and 6-H), 8.39(1H, s, 2'-H), 8.29(1H, d, J = 5 Hz, 6'-H), 7.53(2H, d, J = 5.5 Hz, 3- and 5-H), 7.09(1H, d, J = 5 Hz, 5'-H), 2.64(6H, s, $-N(CH_3)_2$). MS m/z: 199(M^+,100), 198(50). Anal. Calcd. for $C_{24}H_{19}N_9O_{14}$: C, 43.84; H, 2.91; N, 19.18. Found: C, 44.04; H, 2.85; N, 18.96.

4-(3-Dimethylamino-6-pyridyl)pyridine (4g$_6$')

^{1}H-NMR: δ 8.62(2H, d, J = 5 Hz, 2- and 6-H), 8.24(1H, d, J = 3 Hz, 2'-H), 7.84(2H,

d, J = 5 Hz, 3- and 5-H), 7.67 (1H, d, J = 9 Hz, 5'-H), 7.02(1H, dd, J = 9, 3 Hz, 4'-H), 3.06(6H, s, $-N(CH_3)_2$). MS m/z: 199(M^+, 100), 198(83). Anal. Calcd. for $C_{12}H_{13}N_3$: C, 72.33; H, 6.57; N, 21.09. Found: C, 72.42; H, 6.55; N, 20.84.

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