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Condensed Heteroaromatic Ring Systems. XV.[1] Synthesis of Pyranopyridinones from Halopyridinecarbonitriles

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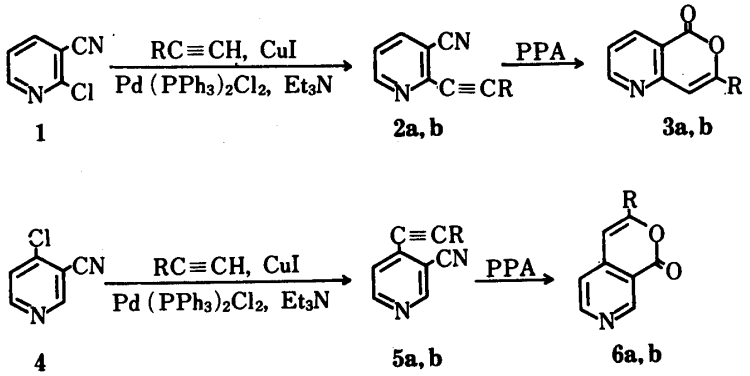
Four kinds of pyranopyridinones were synthesized from pyridinecarbonitriles containing a chlorine or bromine substituent at the adjacent position to the cyano group by the palladium-catalyzed cross-coupling reaction with terminal acetylenes followed by intramolecular cyclization with polyphosphoric acid.

Keywords——halopyridinecarbonitrile; terminal acetylene; palladium-catalyzed reaction; ethynylpyridinecarbonitrile; polyphosphoric acid; pyranopyridinone

Previously, we have reported that 2-ethynylbenzonitriles and ethyl 2-ethynylbenzoates, prepared by the palladium-catalyzed cross-coupling of 2-halobenzonitriles and ethyl 2-halobenzoate with terminal acetylenes, cyclized smoothly to give 3-substituted isocoumarins under acidic conditions in the presence of mercuric sulfate.[2] As an extension of the investigation, we have accomplished a facile synthesis of pyranopyidinones from halopyridinecarbonitriles, which is the subject of the present paper.

The reaction of 2-chloropyridine-3-carbonitrile (**1**) with phenylacetylene in triethylamine in the presence of dichlorobis(triphenylphosphine)palladium and cuprous iodide gave 2-phenylethynylpyridine-3-carbonitrile (**2a**) in satisfactory yield. 7-Phenyl-5*H*-pyrano[4,3-*b*]-pyridin-5-one (**3a**) was obtained by treatment of **2a** with polyphosphoric acid (PPA), although the cyclization with mercuric sulfate in sulfuric acid failed. As well as the above reaction, the cross-coupling reaction of **1** with 1-hexyne and the subsequent cyclization proceeded smoothly, and 7-butyl-5*H*-pyrano[4,3-*b*]pyridin-5-one (**3b**) was obtained in 41% overall yield from **1**.

Additionally, the cyclization of 2-(trimethylsilylethynyl)pyridine-3-carbonitrile with



a : R=Ph **b** : R=Bu

Chart 1

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PPA to the unsubstituted compound (**3**, R=H) was tested, but only a resinous material was obtained.

Similarly, 4-chloropyridine-3-carbonitrile (**4**) reacted smoothly with phenylacetylene and 1-hexyne to give 4-(phenylethynyl)- (**5a**) and 4-(1-hexynyl)pyridine-3-carbonitrile (**5b**), which underwent the cyclization with PPA to give 3-phenyl- (**6a**) and 3-butyl-1*H*-pyrano[3,4-*c*]pyridin-1-one (**6b**), respectively.

Under the same conditions as in the above experiment, the reaction of 3-chloropyridine-4-carbonitrile (**7**) with phenylacetylene or 1-hexyne gave the 3-ethynylpyridine-4-carbonitriles (**9a, b**) in poor yields. When 3-bromopyridine-4-carbonitrile (**8**) was employed instead of **7**, the yields of **9a, b** were improved remarkably. These results suggested that **7** seems to have only insufficient reactivity in the palladium-catalyzed reaction. Almost no difference between **5a, b** and **9a, b** in the cyclization with PPA was observed, and 3-phenyl- (**10a**) and 3-butyl-1*H*-pyrano[4,3-*c*]pyridin-1-one (**10b**) were obtained in 52 and 74% yields, respectively.

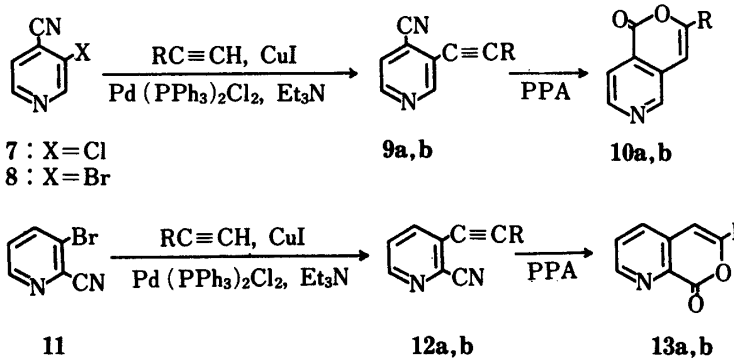

Chart 2

TABLE I. Yields and Spectral Data for Ethynylpyridinecarbonitriles

No.	Yield (%)	IR cm^{-1} ($CHCl_3$)	^{1}H-NMR δ (ppm) ($CDCl_3$)
2a	68	2215	7.2—7.5 (4H, m), 7.5—7.9 (2H, m), 7.95 (1H, dd, J=2, 7), 8.75 (1H, dd, J=2, 5)
2b	68	2230	0.95 (3H, t, J=7), 1.2—2.0 (4H, m), 2.55 (2H, t, J=7), 7.30 (1H, dd, J=5, 7), 7.95 (1H, dd, J=2, 7), 8.70 (1H, dd, J=2, 5)
5a	74	2170 2210	7.3—7.8 (6H, m), 8.70 (1H, d, J=5), 8.82 (1H, s)
5b	73	2220	0.95 (3H, t, J=7), 1.2—2.0 (4H, m), 2.53 (2H, t, J=7), 7.30 (1H, d, J=5), 8.65 (1H, d, J=5), 8.76 (1H, s)
9a	18[a] 79[b]	2170 2210	7.2—7.8 (6H, m), 8.67 (1H, d, J=5), 8.90 (1H, s)
9b	23[a] 92[b]	2230	0.96 (3H, t, J=7), 1.2—2.0 (4H, m), 2.53 (2H, t, J=7), 7.46 (1H, d, J=5), 8.63 (1H, d, J=5), 8.80 (1H, s)
12a	88	2180 2220	7.0—7.8 (6H, m), 7.90 (1H, dd, J=2, 7), 8.60 (1H, dd, J=2, 7)
12b	93	2235	0.96 (3H, t, J=7), 1.2—2.0 (4H, m), 2.50 (2H, t, J=7), 7.41 (1H, dd, J=5, 7), 7.80 (1H, dd, J=2, 7), 8.55 (1H, dd, J=2, 5)

a) Yield from **7**. *b*) Yield from **8**.

These findings suggested that in the reaction of β-halopyridines, the use of bromides was necessary in order to introduce an ethynyl group in a practical manner, while chlorides are reactive enough in the reaction of α- and γ-halopyridines. Thus, 3-bromopyridine-2-carbonitrile (**11**) was allowed to react with phenylacetylene and 1-hexyne under the same

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TABLE II. Yields and Spectral Data for Pyranopyridinones

No	Yield (%)	IR cm^{-1} ($CHCl_3$)	^{1}H-NMR δ (ppm) ($CDCl_3$)
3a	61	1745	7.20 (1H, s), 7.3—7.7 (4H, m), 7.7—8.1 (2H, m), 8.53 (1H, dd, J=2, 7), 8.93 (1H, dd, J=2, 5)
3b	62	1735	0.95 (3H, t, J=7), 1.2—2.0 (4H, m), 2.60 (2H, t, J=7), 6.52 (1H, s), 7.40 (1H, dd, J=5, 7), 8.52 (1H, dd, J=2, 7), 8.90 (1H, dd, J=2, 5)
6a	61	1740	6.90 (1H, s), 7.4—7.7 (4H, m), 7.8—8.1 (2H, m), 8.82 (1H, d, J=5), 9.46 (1H, s)
6b	35	1740	0.98 (3H, t, J=7), 1.2—2.0 (4H, m), 2.53 (2H, t, J=7), 6.12 (1H, s), 7.10 (1H, d, J=5), 8.66 (1H, d, J=5), 9.27 (1H, s)
10a	52	1740	7.00 (1H, s), 7.3—7.7 (3H, m), 7.7—8.2 (3H, m), 8.75 (1H, d, J=5), 8.95 (1H, s)
10b	74	1740	0.96 (3H, t, J=7), 1.2—2.0 (4H, m), 2.60 (2H, t, J=7), 6.38 (1H, s), 8.05 (1H, d, J=7), 8.77 (1H, d, J=5), 8.88 (1H, s)
13a	54	1745	6.90 (1H, s), 7.3—7.7 (3H, m), 7.7—8.1 (4H, m), 8.80 (1H, dd, J=2, 5)
13b	62	1745	0.95 (3H, t, J=7), 1.2—2.0 (4H, m), 2.60 (2H, t, J=7), 6.33 (1H, s), 7.65 (1H, dd, J=5, 7), 7.80 (1H, dd, J=2, 7), 8.86 (1H, dd, J=2, 5)

conditions, and 3-ethynylpyridine-2-carbonitriles (**12a**, **b**) were obtained in good yields as expected. 6-Phenyl- (**12a**) and 6-butyl-8*H*-pyrano-[3,4-*b*]pyridin-8-one (**13a**, **b**) were obtained by the same procedure as described above.

There are few papers dealing with the covenient synthesis of pyranopyridines. For example, 2-styrylpyridine-3-carboxylic acid prepared by the condensation of 2-methylpyridine-3-carboxylic acid with benzaldehyde was transformed into 7-phenyl-5*H*-pyrano[4,3-*b*]pyridin-5-one, but the condensation was reported to result in a poor yield (5%) of the styrylpyridine.[3] As reported by Kametani *et al.*,[4] 4-methylpyridine-3-carbonitrile reacted with diethyl oxalate in the presence of potassium *tert*-butoxide, but the yield of the condensation product, ethyl 1-oxo-1*H*-pyrano[3,4-*c*]pyridine-3-carboxylate, was 10%.

In conclusion, our present results provide a general method for the synthesis of substituted pyranopyridinones. Since it is well known that isocoumarins react with ammonia and primary amines to give isoquinolinones, the pyranopyridinones described in this paper are considered to be favorable substrates for the synthesis of naphthyridinones.

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer. Chemical shifts are expressed in δ (ppm) values, and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s=singlet, d=doublet, dd=double doublet, t=triplet, and m=multiplet.

Starting halopyridinecarbonitriles except for 3-bromopyridine-4-carbonitrile (**8**) were synthesized according to the reported procedures: 2-chloropyridine-3-carbonitrile (**1**),[5] 4-chloropyridine-3-carbonitrile (**4**),[6] 3-chloropyridine-4-carbonitrile (**7**),[7] and 3-bromopyridine-2-carbonitrile (**11**).[8]

3-Bromopyridine-4-carbonitrile (8)——A mixture of 3-bromo-4-methylpyridine (8.6 g, 50 mmol) and liquid NH_3-KNH_2 [prepared from liquid NH_3 (300 ml) and K (3.9 g, 100 mmol)] was stirred at −33 °C for 2h, then propyl nitrate (8.9 g, 100 mmol) was added. The mixture was stirred at −33 °C for 3 h and quenched with NH_4Cl. After evaporation of the NH_3, the residue was extracted with hot acetone. The residue obtained from the acetone extract was added to a solution of $POCl_3$ (100 ml) and $CHCl_3$ (100 ml), and the mixture was refluxed for 3 h. Evaporation of the $CHCl_3$ and the excess $POCl_3$ gave the residue, which was poured into cold 30% aqueous NH_3 and extracted with $CHCl_3$. The residue obtained from the $CHCl_3$ extract was purified by silica gel column chromatography using C_6H_6 as an eluent. The product was recrystallized from hexane-ether to give pale yellow needles, mp 93 °C (lit.[9] mp 94 °C). Yield 4.63 g (41%). IR ($CHCl_3$) cm^{-1}: 2240. ^{1}H-NMR (CCl_4): 7.56 (1H, d, J=5), 8.66 (1H, d, J=5), 8.91 (1H, s).

General Procedure for the Syntheses of Ethynylpyridinecarbonitriles——A mixture of a halopyridinecarbonitrile (10 mmol), an acetylene (12 mmol), Pd $(PPh_3)_2Cl_2$ (160 mg), CuI (80 mg), and Et_3N (2 ml) was heated in a sealed tube at 120 °C for 4—6 h. In the reaction of 3-chloropyridine-4-carbonitrile (**7**), dimethylformamide (2 ml) was used as a

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Table III. Physical Constants and Analytical Data for Ethynylpyridinecarbonitriles

No.	mp or bp/mmHg (°C)	Appearance (Recrystal. solvent)	Formulae	Analysis (%) Calcd (Found)		
				C	H	N
2a	85—87	Colorless needles (ether–hexane)	$C_{14}H_8N_2$	82.34 (82.59	3.95 4.06	13.72 13.46)
2b	135/3	Colorless liquid	$C_{12}H_{12}N_2$	78.23 (78.16	6.56 6.72	15.20 15.07)
5a	170/3 85—87	Colorless needles (hexane)	$C_{14}H_8N_2$	82.34 (82.37	3.95 3.89	13.72 13.54)
5b	130/3	Colorless liquid	$C_{12}H_{12}N_2$	78.23 (78.53	6.56 6.45	15.20 15.27)
9a	150/3 49—53	Colorless solid	$C_{14}H_8N_2$	82.34 (82.58	3.95 3.88	13.72 13.48)
9b	135/3	Colorless liquid	$C_{12}H_{12}N_2$	78.23 (78.15	6.56 6.32	15.20 14.69)
12a	180/3 60—62	Colorless needles (hexane)	$C_{14}H_8N_2$	82.34 (82.23	3.95 3.76	13.72 13.59)
12b	135/3	Colorless liquid	$C_{12}H_{12}N_2$	78.23 (78.51	6.56 6.60	15.20 15.10)

Table IV. Physical Constants and Analytical Data for Pyranopyridinones

No.	mp or bp/mmHg (°C)	Appearance (Recrystal. solvent)	Formulae	Analysis (%) Calcd (Found)		
				C	H	N
3a	134—135[a)]	Colorless needles (ether–hexane)	$C_{14}H_{10}NO_2$	75.33 (75.59	4.06 3.77	6.27 6.30)
3b	150/3	Colorless solid	$C_{12}H_{13}NO_2$	70.92 (71.13	6.45 6.46	6.89 6.85)
6a	142—143	Colorless needles (ether–hexane)	$C_{14}H_{10}NO_2$	75.33 (75.52	4.06 4.01	6.27 6.29)
6b	130—135/3	Colorless liquid	$C_{12}H_{13}NO_2$	70.92 (71.09	6.45 6.50	6.89 6.91)
10a	166—168	Colorless scales (ether–hexane)	$C_{14}H_{10}NO_2$	75.33 (75.28	4.06 4.01	6.27 6.23)
10b	155/3	Colorless solid	$C_{12}H_{13}NO_2$	70.92 (70.91	6.45 6.54	6.89 6.72)
13a	141—143	Colorless prisms (C_6H_6)	$C_{14}H_{10}NO_2$	75.33 (75.24	4.06 3.83	6.27 6.17)
13b	165/3	Colorless liquid	$C_{12}H_{13}NO_2$	70.92 (70.72	6.45 6.48	6.89 7.01)

a) Lit.[3] mp 128—129 °C.

solvent, and the mixture was heated for 20—24 h. The reaction mixture was diluted with H_2O and extracted with ether. The residue was purified by silica gel column chromatography using hexane–C_6H_6 (2 : 1, v/v) as an eluent. The product was distilled under reduced pressure or recrystallized from the solvent shown in Table III.

General Procedure for the Syntheses of Pyranopyridinones——A mixture of an ethynylpyridinecarbonitrile (2 mmol) and PPA (8.0 g) was heated at 130 °C for 15 min, poured into ice-water, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The residue obtained from the $CHCl_3$ extract was purified by silica gel column chromatography using hexane–acetone (19 : 1, v/v) as an eluent. The product was distilled under reduced pressure or recrystallized from the solvent shown in Table IV.

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