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Studies on Quinoline and Isoquinoline Derivatives. II.[1] Coupling Reaction of Haloquinolines and Haloisoquinolines with Monosubstituted Acetylenes in the Presence of Palladium Complex

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The quinoline, isoquinoline, and acridine derivatives containing an acetylenic side chain at the pyridine moiety were synthesized by means of coupling reaction of alkyl (or phenyl) acetylenes with the corresponding halogeno derivatives in the presence of a palladium triphenylphosphine complex.

Keywords——alkynylquinoline; alkynylisoquinoline; 9-phenylethynylacridine; acetylene coupling reaction; palladium triphenylphosphine complex

Previously, we have reported[3] that 2-, 4-, and 5-iodopyrimidines readily reacted with monosubstituted acetylenes in the presence of cuprous iodide and a palladium complex,[4] prepared from palladium dichloride and triphenylphosphine, in triethylamine giving alkynylpyrimidines. Since the facile way to the synthesis of alkynyl derivatives of monoazaheteroaromatics such as quinoline, isoquinoline, and acridine had not been opened,[5] the authors studied the application of this method to the preparation of the above mentioned compounds.

The halogeno compounds investigated in this research were as follows: 2-iodo- (I),[6] 3-bromo-(II),[7] and 4-iodo-quinoline (III),[8] 1-iodo-(IV),[9] 3-bromo-(V),[10] and 4-iodo-isoquinoline (VI),[11] and 9-iodoacridine (VII).[12] As shown in Chart and Table, the coupling reaction proceeded according to the following manner.

1) The β-halogeno derivatives (II, VI), like α- and γ-substituted compounds (I, III, IV, VII), underwent the coupling reaction in good yield.

2) When the compounds containing an iodine atom at the α- or γ-positions were employed, the reaction proceeded at room temperature. In the case of other compounds (II, V, VI) elevated temperature was necessary to obtain the products.

3) A catalytic amount of the complex was effective enough to bring about the reaction.

4) The experimental simplicity of this coupling reaction and the yields of the products, with a few exception, were both satisfactory.

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Accordingly, the preparation of acetylenic N-heteroaromatics might be focussed on the synthetic availability of halogenides.

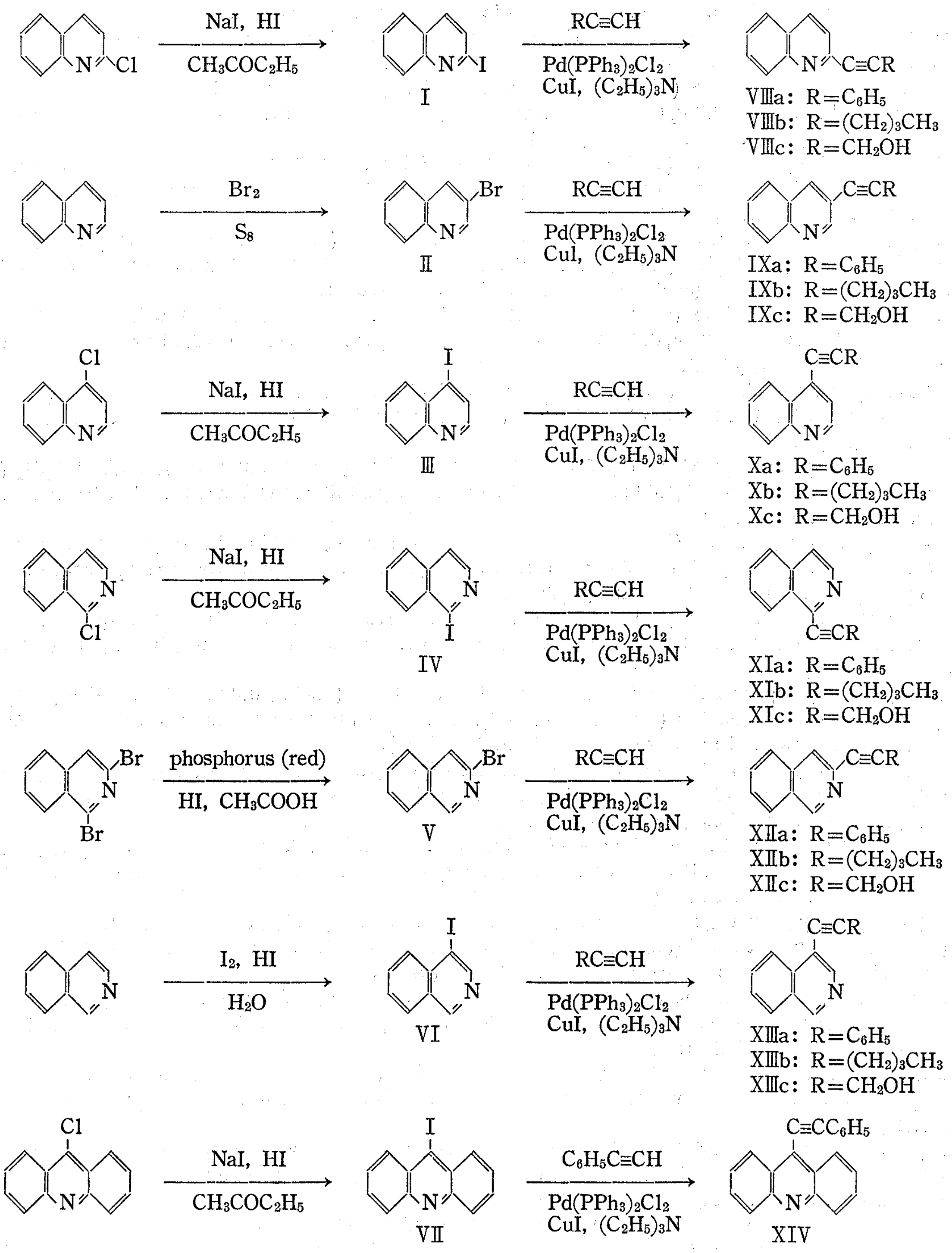

Chart 1

Experimental[13]

General Procedure of Coupling Reaction——Halogeno N-heteroaromatics (0.006 mol) and acetylenes (0.009 mol) were dissolved in triethylamine (40 ml) with a catalytic amount of $Pd(PPh_3)_2Cl_2$ (0.1 mmol)

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[13] All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer.

and CuI (0.2 mmol). After the mixture has been stirred at proper temperature for proper hours, the reaction mixture was concentrated to dryness under reduced pressure. A proper quantity of water (30—40 ml) was added to the residue and the aqueous layer was made alkaline with potassiun carbonate and extracted with benzene or chloroform. The benzene or chloroform extract was passed through a short column (Al_2O_3) to remove the catalyst. Evaporation of the benzene or chloroform gave the crude products which were purified by vacuum distillation or (and) recrystallization.

2-Phenylethynylquinoline (VIIIa)——A mixture of I (1.90 g, 0.007 mol), $Pd(PPh_3)_2Cl_2$ (70 mg), CuI (35 mg), phenylacetylene (0.8 g, 0.008 mol), and Et_3N (40 ml) was kept at room temperature for 7 hr to give yellow needles (hexane). Yield 1.60 g (94%).

2-*n*-Butylethynylquinoline (VIIIb)——A mixture of I (1.60 g, 0.006 mol), $Pd(PPh_3)_2Cl_2$ (70 mg), CuI (35 mg), 1-hexyne (0.8 g, 0.01 mol), and Et_3N (40 ml) was kept at room temperature for 16 hr to give a pale yellow liquid. Yield 0.67 g (52%).

3-(2-Quinolyl)propargyl Alcohol (VIIIc)——A mixture of I (1.60 g, 0.006 mol), $Pd(PPh_3)_2Cl_2$ (70 mg), CuI (35 mg), propargyl alcohol (0.60 g, 0.01 mol), and Et_3N (40 ml) was kept at room temperature for 3.5 hr to give pale yellow prisms (acetone–ether). Yield 0.15 g (12%).

3-Phenylethynylquinoline (IXa)——A mixture of II (1.25 g, 0.006 mol), $Pd(PPh_3)_2Cl_2$ (70 mg), CuI (35 mg), phenylacetylene (0.80 g, 0.008 mol), and Et_3N (40 ml) was refluxed for 17.5 hr to give colorless prisms (hexane). Yield 0.80 g (58%).

3-*n*-Butylethynylquinoline (IXb)——A mixture of II (2.50 g, 0.012 mol), $Pd(PPh_3)_2Cl_2$ (150 mg), CuI (75 mg), 1-hexyne (1.64 g, 0.02 mol), and Et_3N (60 ml) was refluxed for 20 hr to give a pale yellow liquid. Yield 1.53 g (54%).

3-(3-Quinolyl)propargyl Alcohol (IXc)——A mixture of II (2.50 g, 0.012 mol), $Pd(PPh_3)_2Cl_2$ (150 mg), CuI (75 mg), propargyl alcohol (1.60 g, 0.029 mol), and Et_3N (60 ml) was refluxed for 10 hr to give pale yellow needles. Yield 1.30 g (59%).

4-Phenylethynylquinoline (Xa)——A mixture of III (1.50 g, 0.006 mol), $Pd(PPh_3)_2Cl_2$ (70 mg), CuI (35 mg), phenylacetylene (0.80 g, 0.008 mol), and Et_3N (40 ml) was kept at room temperature for 16 hr to give a pale yellow liquid. Yield 1.25 g (93%).

4-*n*-Butylethynylquinoline (Xb)——A mixture of III (1.50 g, 0.006 mol), $Pd(PPh_3)_2Cl_2$ (70 mg), CuI (35 mg), 1-hexyne (0.80 g, 0.01 mol), and Et_3N (40 ml) was refluxed for 4 hr to give a pale yellow liquid. Yield 0.93 g (76%).

3-(4-Quinolyl)propargyl Alcohol (Xc)——A mixture of III (1.50 g, 0.006 mol), $Pd(PPh_3)_2Cl_2$ (70 mg), CuI (35 mg), propargyl alcohol (0.60 g, 0.011 mol), and Et_3N (40 ml) was warmed at 35—40° for 6 hr to give colorless needles (acetone–hexane). Yield 0.65 g (59%).

1-Phenylethynylisoquinoline (XIa)——A mixture of IV (1.50 g, 0.006 mol), $Pd(PPh_3)_2Cl_2$ (70 mg), CuI (35 mg), phenylacetylene (0.80 g, 0.008 mol), and Et_3N (40 ml) was kept at room temperature for 13.5 hr to give pale yellow needles (benzene–ether). Yield 1.20 g (87%).

1-*n*-Butylethynylisoquinoline (XIb)——A mixture of IV (1.50 g, 0.006 mol), $Pd(PPh_3)_2Cl_2$ (70 mg), CuI (35 mg), 1-hexyne (0.80 g, 0.01 mol), and Et_3N (40 ml) was kept at room temperature for 15 hr to give a pale yellow liquid. Yield 1.05 g (85%).

3-(1-Isoquinolyl)propargyl Alcohol (XIc)——A mixture of IV (1.50 g, 0.006 mol), $Pd(PPh_3)_2Cl_2$ (70 mg), CuI (35 mg), propargyl alcohol (0.60 g, 0.011 mol), and Et_3N (40 ml) was warmed at 35—40° for 8 hr to give pale yellow needles (acetone-hexane). Yield 0.70 g (64%).

3-Phenylethynylisoquinoline (XIIa)——A mixture of V (1.25 g, 0.006 mol), $Pd(PPh_3)_2Cl_2$ (70 mg), CuI (35 mg), phenylacetylene (0.90 g, 0.009 mol), and Et_3N (40 ml) was refluxed for 12 hr to give colorless needles (acetone–ether). Yield 1.23 g (89%).

3-*n*-Butylethynylisoquinoline (XIIb)——A mixture of V (1.25 g, 0.006 mol), $Pd(PPh_3)_2Cl_2$ (70 mg), CuI (35 mg), 1-hexyne (0.90 g, 0.011 mol), and Et_3N (40 ml) was refluxed for 12 hr to give colorless prisms (hexane). Yield 1.10 g (87%).

3-(3-Isoquinolyl)propargyl Alcohol (XIIc)——A mixture of V (1.25 g, 0.006 mol), $Pd(PPh_3)_2Cl_2$ (70 mg), CuI (35 mg), propargyl alcohol (0.60 g, 0.011 mol), and Et_3N (40 ml) was refluxed for 13 hr to give pale yellow needles (AcOEt). Yield 0.40 g (36%).

4-Phenylethynylisoquinoline (XIIIa)——A mixture of VI (1.53 g, 0.006 mol), $Pd(PPh_3)_2Cl_2$ (70 mg), CuI (35 mg), phenylacetylene (0.90 g, 0.009 mol), and Et_3N (40 ml) was kept at room temperature for 3.5 hr to give colorless needles (ether–hexane). Yield 1.25 g (91%).

4-*n*-Butylethynylisoquinoline (XIIIb)——A mixture of VI (1.53 g, 0.006 mol), $Pd(PPh_3)_2Cl_2$ (70 mg), CuI (35 mg), 1-hexyne (0.90 g, 0.011 mol), and Et_3N (40 ml) was refluxed for 8 hr to give a pale yellow liquid. Yield 0.85 g (69%).

3-(4-Isoquinolyl)propargyl Alcohol (XIIIc)——A mixture of VI (1.53 g, 0.006 mol), $Pd(PPh_3)_2Cl_2$ (70 mg), CuI (35 mg), propargyl alcohol (0.50 g, 0.009 mol), and Et_3N (40 ml) was refluxed for 2.5 hr to give pale yellow needles. Yield 0.53 g (43%).

9-Phenylethynylacrydine (XIV)——A mixture of VII (3.1 g, 0.01 mol), $Pd(PPh_3)_2Cl_2$ (80 mg), CuI (40 mg), phenylacetylene (1.2 g, 0.012 mol), and Et_3N (80 ml) was kept at room temperature for 10 hr to give pale yellow needles. Yield 2.20 g (78%).

TABLE I. Acetylenic N-Heteroaromatics

No.	mp (°C)	bp (mmHg) (°C)	IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}	Formula	Analysis (%) Calcd. (Found)		
					C	H	N
VIIIa	66—67	175—185 (3)	2230	$C_{17}H_{11}N$	89.05 (88.81	4.84 4.96	6.11 6.13)
VIIIb	—	153 (3)	2240	$C_{15}H_{15}N$	86.05 (86.32	7.22 7.46	6.69 6.64)
VIIIc	86—87	—	2240	$C_{12}H_9NO \cdot 1/4H_2O$	76.78 (76.95	5.10 5.01	7.46 7.29)
IXa	80—81.5	175—180 (3)	2240	$C_{17}H_{11}N$	89.05 (88.98	4.84 4.87	6.11 5.68)
IXb	—	170—175 (3)	2240	$C_{15}H_{15}N$	86.05 (85.81	7.22 7.27	6.69 6.42)
IXc	126—127	—	2240	$C_{12}H_9NO$	78.67 (78.86	4.95 4.91	7.65 7.48)
Xa	—	174 (3)	2240	$C_{17}H_{11}N$	89.05 (88.59	4.84 5.08	6.11 6.11)
Xb	—	143 (3)	2235	$C_{15}H_{15}N$	86.08 (85.32	7.22 7.19	6.69 6.48)
Xc	142—144	—	2220	$C_{12}H_9NO$	78.67 (78.77	4.95 4.98	7.65 7.47)
XIa	97—98	183 (3)	2220	$C_{17}H_{11}N$	89.05 (88.84	4.84 4.89	6.11 6.00)
XIb	—	158 (3)	2230	$C_{15}H_{15}N$	86.08 (85.86	7.22 7.16	6.69 6.67)
XIc	114—115	—	2240	$C_{12}H_{19}NO \cdot 1/2H_2O$	74.98 (75.00	5.24 5.13	7.29 7.42)
XIIa	86—86.5	198 (1)	2215	$C_{17}H_{11}N$	89.05 (89.13	4.84 4.84	6.11 6.05)
XIIb	36—37	165—167 (1)	2220	$C_{15}H_{15}N$	86.08 (85.87	7.22 7.26	6.69 6.53)
XIIc	126.5—127.5	—	—	$C_{12}H_9NO$	78.67 (78.37	4.95 4.95	7.65 7.38)
XIIIa	60—62	220—225 (3)	2215	$C_{17}H_{11}N$	89.05 (88.93	4.84 4.89	6.11 5.87)
XIIIb	—	220 (3)	2240	$C_{15}H_{15}N$	86.08 (85.65	7.22 7.55	6.69 6.63)
XIIIc	142—143	—	—	$C_{12}H_9NO$	78.67 (78.77	4.95 4.98	7.65 7.47)
XIV	166—167.5	—	2200	$C_{21}H_{13}N$	90.29 (90.10	4.69 4.69	5.02 4.99)

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