Acetylene Chemistry. Part 27 [1]. Palladium Catalysed C-C Bond Formation Between Quinoline and Mono-substituted Alkynes: Synthesis of 4-Alkynyl-2-bromoquinolines

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Six new 4-alkynyl-2-bromoquinolines have been synthesised *via* palladium catalysed C-C bond formation between 2,4-dibromoquinoline and mono-substituted alkynes. Position of the alkyne substituent was confirmed to be at C-4 by an nOe experiment on some methoxy derivatives prepared by nucleophilic displacement of bromo substituent.

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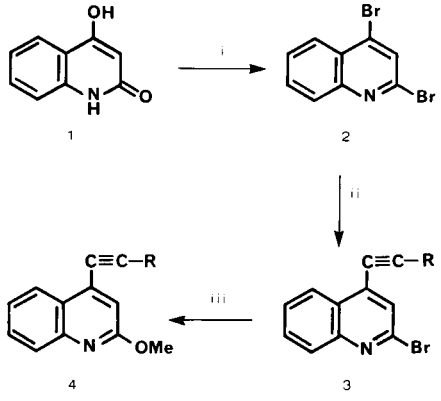
An array of biological activities such as anti-malarial, anti-fungal, insecticidal, herbicidal and anti-tumor has been reported to be shown by various haloquinolines [2]. It has been proved that 2-chloroquinoline to be effective in the control of human body lice [3], while several 2-, 4- and 8-haloquinolines have been used in the control of aphides [4]. It is apparent that some haloquinolines show plant growth regulating activity. Early sprouting of seed potatoes could be prevented by the use of 2- and 6-chloroquinolines [5] while it has been shown that 2-chloro-4-methylquinoline is effective as a plant growth inhibitor [6]. Various alkynylquinolines have been considered for use as bactericides [7], insecticides [8], pesticides [9], fungicides [10], analgesics [8,11], and intermediates for the preparation of vinyl compounds and in the pharmaceutical and cosmetic industries [7,9]. Prompted by these claims and in continuing our synthetic studies on bioactive heterocyclics and acetylenes, we have now synthesized six new 4-alkynyl-2-bromoquinolines *via* palladium catalysed C-C bond formation in a single step.

The starting material used in this reaction was 2,4-dibromoquinoline (**2**) and it was quantitatively prepared from 4-hydroxy-2(1*H*)-quinolinone (**1**). Treatment of 2,4-dibromoquinoline (**2**) with monosubstituted alkynes in the presence of bis(triphenylphosphine)palladium(II) chloride and catalytic amount of copper(I) iodide yielded bromo alkynyl quinolines exclusively; one of the bromo substituents has been replaced by the alkynyl substituent.

Scheme. Synthesis of 2-Bromo-4-alkynylquinoline and 2-Methoxy-4-alkynylquinoline Derivatives



4a, R = -Ph
4b, R = -C(OH)Ph
Me
4d, R = -CH(OH)Me

3a, R = -Ph
3b, R = -C(OH)Ph
Me
3c, R = $-CO_2Et$
3d, R = -CH(OH)Me
3e, R = $-C(NH_2)Me_2$
3f, R = $-(CH_2)_7CH_3$

i, $POBr_3/\Delta$; ii, H-C≡C-R/$Pd(PPh_3)_2Cl$/CuI/reflux/2 hours; iii, NaOMe/MeOH

The position of the alkynyl substituent was confirmed by preparing alkynylmethoxyquinolines from a few selected alkynylbromoquinolines through direct nucleophilic displacement by the treatment with sodium methoxide in anhydrous methanol and carrying out an nOe experiment. The nOe difference spectra at 300 MHz showed enhancement only for 3-*H* signal of the foregoing alkynylmethoxyquinolines, upon irradiation at the -O*Me* signal. This revealed that the alkynyl substituent is situated at C-4 of the quinoline nucleus.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ^1H nmr spectra were recorded in deuteriochloroform with TMS as the internal reference on a Varian Gemini 200 spectrometer while the nOe experiments were carried out on a Bruker WM 300 spectrometer. Mass spectra were obtained on a Varian MAT 44S instrument at 70 eV.

Preparation of 2,4-Dibromoquinoline (**2**).

2,4-Dibromoquinoline (**2**) was prepared quantitatively by the treatment of 4-hydroxy-2(1*H*)-quinolinone (**1**) with excess phosphorus oxybromide, mp 90-91°; ^1H nmr: δ 8.50-7.96 (m, 2H, ArH), 7.80 (s, 1H, 3-*H*), 7.78-7.50 (m, 2H, ArH); ^{13}C nmr: δ 148.28 (C-8a), 140.38 (C-2), 134.84 (C-4), 131.20 (C-7), 128.83 (C-5), 128.44 (C-6), 127.96 (C-8), 126.58 (C-3), 126.29 (C-4a); ms: m/z (% relative intensity) 289 (28), 287 (57), 285 (M^+, 31), 208 (M^+-Br, 51), 127 (M^+-2Br, 100), 100 (43), 74 (69), 63 (34).

Preparation of 2-Bromo-4-alkynylquinoline Derivatives **3**.

2,4-Dibromoquinoline (**2**) (0.430 g, 1.5 mmoles) was dissolved in triethylamine (*ca.* 50 ml) and the terminal alkyne a, or b or c or d or e or f (1.5 mmoles), bis(triphenylphosphine)palladium(II) chloride (0.011 g, 0.015 mmole), Copper(I) iodide (*ca.* 0.010 g) were added and heated the mixture under reflux for 2 hours. The reaction mixture was filtered, the solvent, triethylamine was evaporated *in vacuo*. The residue was redissolved in dichloromethane and filtered. The filtrate was evaporated and the product was isolated and purified successively by chromatography (silica gel column and/or preparative thin layer chromatography) and recrystallisation.

1-(2′-Bromo-4′-quinolyl)-2-phenylacetylene (**3a**).

This compound was obtained as a colourless solid (0.201 g, 43%) on successive column chromatography and preparative tlc (eluant: light petroleum/dichloromethane 2:1), colourless needles from light petroleum, mp 103°; ^{1}H nmr: δ 8.16 (dd, 1H, J = 1.5 and 8.2 Hz, 5-*H*), 8.13 (dd, 1H, J = 1.3 and 8.4 Hz, 8-*H*), 7.92 (s, 1H, 3-*H*), 7.77 (ddd, 1H, J = 1.5, 6.7 and 8.4 Hz, 7-*H*), 7.69-7.59 (m, 3H, Ar*H*), 7.44-7.35 (m, 3H, Ar*H*); ms: m/z (% relative intensity) 309 (90), 307 (M^+, 91), 228 (M^+-Br, 68), 127 (M^+-Br, -C≡CPh, 33), 101 (PhC≡C$^+$, 96), 75 (100) and 63 (22).

Anal. Calcd. for $C_{17}H_{10}BrN$: C, 66.25; H, 3.27; N, 4.54; Br, 25.93. Found: C, 66.32; H, 3.24; N, 4.62; Br, 25.98.

4-(2′-Bromo-4′-quinolyl)-2-phenyl-3-butyn-2-ol (**3b**).

This compound was obtained as a low melting solid (0.247 g, 47%) on successive column and preparative tlc (eluant: 2% methanol in dichloromethane x 2), mp 45-46°; ^{1}H nmr: δ 8.10 (dd, 1H, J = 1.6 and 8.2 Hz, 5-*H*), 8.02 (dd, 1H, J = 1.3 and 8.4 Hz, 8-*H*), 7.75 (s, 1H, 3-*H*), 7.77-7.67 (m, 3H, Ar*H*), 7.60 (ddd, 1H, J = 1.3, 7.0 and 8.2 Hz, 6-*H*), 7.42-7.25 (m, 3H, Ar*H*), 1.93 (s, 3H, *Me*); ms: m/z (% relative intensity) 353 (6), 351 (M^+, 30), 337 (22), 335 (23), 310 (76), 308 (90), 272 (M^+-Br, 16), 245 (22), 229 (38), 177 (13), 166 (24), 127 (33), 99 (100), 84 (74), 77 (74) and 63 (36); hrms Calcd. for $C_{19}H_{14}BrNO$: 351.025874. Found: 351.02624.

Ethyl 3-(2′-Bromo-4′-quinolyl)propynoate (**3c**).

This compound was obtained as a colourless solid (0.053 g, 12%) on column chromatography, colourless needles from light petroleum, mp 102-103°; ^{1}H nmr: δ 8.19 (dd, 1H, J = 1.7 and 8.3 Hz, 5-*H*), 8.13 (dd, 1H, J = 1.4 and 8.5 Hz, 8-*H*), 7.93 (s, 1H, 3-*H*), 7.82 (ddd, 1H, J = 1.7, 6.9 and 8.5 Hz, 7-*H*), 7.71 (ddd, 1H, J = 1.4, 6.9 and 8.3 Hz, 6-*H*), 4.34 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 1.37 (t, 3H, J = 7.1 Hz, OCH_2CH_3); ms: m/z (% relative intensity) 305 (40), 303 (M^+, 34), 260 (68), 258 (100), 233 (96), 231 (86), 206 (12), 208 (12), 152 (38), 151 (50), 127 (37), 101 (30), 89 (18), 75 (71) and 63 (12).

Anal. Calcd. for $C_{14}H_{10}BrNO_2$: C, 55.28; H, 3.31; N, 4.60; Br, 26.27. Found: C, 55.37; H, 3.34; N, 4.69; Br, 26.25.

4-(2′-Bromo-4′-quinolyl)-3-butyn-2-ol (**3d**).

This compound was obtained as a colourless solid (0.273 g, 66%) on successive column and preparative tlc (eluant: 3% methanol in dichloromethane), colourless needles from light petroleum/dichloromethane, mp 110-111°; ^{1}H nmr: δ 8.09 (dd, 1H, J = 1.4 and 8.4 Hz, 5-*H*), 8.07 (dd, 1H, J = 1.3 and 8.4 Hz, 8-*H*), 7.73 (ddd, 1H, J = 1.4, 6.9 and 8.4 Hz, 7-*H*), 7.72 (s, 1H, 3-*H*), 7.60 (ddd, 1H, J = 1.3, 6.9 and 8.4 Hz, 6-*H*), 4.90 (q, 1H, J = 6.7 Hz, -C*H*CH_3), 4.35-4.10 (brs, 1H, O*H*), 1.63 (3H, d, J = 6.7 Hz, -CHCH_3); ms: m/z (% relative intensity) 277 (22), 275 (M^+, 21), 262 (13), 260 (18), 234 (96), 232 (100), 210 (14), 208 (14), 178 (10), 167 (15), 153 (46), 127 (44), 101 (40), 89 (14), 83 (19), 75 (54) and 63 (30).

Anal. Calcd. for $C_{13}H_{10}BrNO$: C, 56.54; H, 3.65; N, 5.07; Br, 28.94. Found: C, 56.48; H, 3.61; N, 4.98; Br, 28.91.

4-(2′-Bromo-4′-quinolyl)-2-methyl-3-butyn-2-amine (**3e**).

This compound was obtained as a pale yellow solid (0.246 g, 57%) on successive column and preparative tlc (eluant: 4% methanol in dichloromethane x 3), pale yellow needles from light petroleum/dichloromethane, mp 94-95°; ^{1}H nmr: δ 8.14 (dd, 1H, J = 8.3 and 1.6 Hz, 5-*H*), 8.08 (dd, 1H, J = 8.4 and 1.3 Hz, 8-*H*), 7.78 (s, 1H, 3-*H*), 7.75 (1H, ddd, J = 8.4, 6.9 and 1.6 Hz, 7-*H*), 7.61 (ddd, 1H, J = 8.3, 6.9 and 1.3 Hz, 6-*H*), 1.55 (s, 6H, 2 x CH_3); ms: m/z (% relative intensity) 290 (5), 288 (M^+, 5), 275 (95), 273 (100), 258 (11), 256 (19), 248 (7), 246 (8), 234 (19), 232 (20), 208 (8), 206 (8), 192 (95), 177 (6), 167 (14), 153 (26), 127 (28), 101 (47), 93 (40), 75 (68), 63 (18) and 51 (47); hrms Calcd. for $C_{14}H_{13}BrN_2$: 288.026208. Found: 288.02666.

1-(2′-Bromo-4′-quinolyl)-1-decyne (**3f**).

This compound was obtained as a pale yellow oil (0.194 g, 38%) on column and preparative tlc (eluant: 10% dichloromethane in light petroleum x 3); ^{1}H nmr: δ 8.14 (dd, 1H, J = 1.6 and 8.5 Hz, 5-*H*), 8.08 (dd, 1H, J = 1.5 and 8.5 Hz, 8-*H*), 7.77 (s, 1H, 3-*H*), 7.75 (ddd, 1H, J = 1.6, 6.9 and 8.5 Hz, 7-*H*), 7.61 (ddd, 1H, J = 1.5, 6.9 and 8.5 Hz, 6-*H*), 2.5 (t, 2H, J = 7.0 Hz, $-CH_2-CH_2-C\equiv C-$), 1.8-1.2 (m, 12H, 6 x CH_2), 0.90 (3H, t, J = 6.9 Hz, $-CH_2-CH_3$); ms: m/z (% relative intensity) 345 (12), 343 (14, M^+), 330 (8), 328 (10, M^+-CH_3), 316 (24), 314 (24), 302 (70), 300 (76), 288 (82), 286 (82), 274 (40), 272 (60), 260 (98), 258 (100), 247 (82), 245 (80), 222 (46), 208 (24), 178 (36), 165 (80), 152 (24), 138 (60), 127 (34), 101 (62) and 75 (98); hrms Calcd. for $C_{19}H_{22}BrN$: 343.09355. Found: 343.09376.

Preparation of 2-Methoxy-4-alkynylquinoline Derivatives **4**.

The foregoing 2-bromo-4-alkynylquinoline derivatives **3a**, **3b** and **3d** (40 mg) were dissolved in dry methanol and sodium methoxide was added (excess) and heated under reflux for 1-8 hours (reaction was monitored by tlc). The reaction mixture was concentrated *in vacuo*, diluted with water and extracted with dichloromethane. The dichloromethane was evaporated and the product purified by preparative tlc (eluant: 4% methanol in dichloromethane).

1-(2′-Methoxy-4′-quinolyl)-2-phenylacetylene (**4a**).

This compound was obtained as colourless needles from dichloromethane/light petroleum, mp 128-130°; ^{1}H nmr: δ 8.16 (dd, 1H, J = 1.5 and 8.2 Hz, 5-*H*), 8.06 (dd, 1H, J = 1.3 and 8.3 Hz, 8-*H*), 7.71-7.75 (m, 3H, Ar*H*), 7.50 (ddd, 1H, J = 1.5, 6.7 and 8.4 Hz, 7-*H*), 7.40-7.37 (m, 3H, Ar*H*), 6.98 (s, 1H, 3-*H*), 4.07 (s, 3H, OCH_3); the peak at δ 6.98 was enhanced when the peak at δ 4.07 was irradiated during the nOe experiment; ms: m/z (% relative intensity) 259 (M^+, 100), 230 (13), 216 (14), 129 (14), 105 (15), 89 (16), 77 (18), 63 (14) and 51 (16); hrms Calcd. for $C_{18}H_{13}NO$: 259.09979. Found: 259.09968.

4-(2′-Methoxy-4′-quinolyl)-2-phenyl-3-butyn-2-ol (**4b**).

The compound was obtained as a colourless oil; ^{1}H nmr: δ 8.14-8.01 (m, 2H, Ar*H*), 7.80-7.65 (m, 3H, Ar*H*), 7.52-7.31 (m, 4H,

Ar*H*), 6.87 (s, 1H, 3-*H*), 4.03 (s, 3H, OCH_3); the peak at δ 6.87 was enhanced when the peak at δ 4.03 was irradiated during the nOe experiment; ms: m/z (% relative intensity) 303 (10), 288 (38), 260 (100), 245 (12), 215 (25), 184 (8), 130 (10), 105 (23), 77 (58); hrms Calcd. for $C_{20}H_{17}NO_2$: 303.125929. Found: 303.12638.

4-(2'-Methoxy-4-quinolyl)-3-butyn-2-ol (**4d**).

This compound was obtained as a colourless semisolid; ^{1}H nmr: δ 8.35 (dd, 1H, J = 1.4 and 8.4 Hz, 5-*H*), 8.20 (dd, 1H, J = 1.3 and 8.4 Hz, 8-*H*), 7.95 (ddd, 1H, J = 1.4, 6.9 and 8.4 Hz, 7-*H*), 7.80 (ddd, 1H, J = 1.3, 6.9 and 8.4 Hz, 6-*H*), 5.9 (s, 1H, 3-*H*), 4.00 (s, 3H, OCH_3), 4.90 (q, 1H, J = 6.7 Hz, -C*H*CH$_3$), 1.70 (d, 3H, J = 6.7 Hz, -CHCH_3); the peak at δ 5.9 was enhanced when the peak at δ 4.00 was irradiated during the nOe experiment.

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REFERENCES AND NOTES

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[1] Part **26**: J. Reisch, A. R. Ram Rao and C. O. Usifoh, *Chem. Mon.*, in press.

[2] R. K. Smalley, Heterocyclic Compounds, Vol **32**, G. Jones, ed, John Wiley and Sons, New York, 1977, p 319.

[3] G. W. Eddy and N. B. Carson, *J. Econ. Entomol.*, **39**, 763 (1946).

[4] Wm. A. Knapp, U. S. Patent 2,427,677 (1948); *Chem. Abstr.*, **42**, 318 (1948).

[5] F. E. Denny, U. S. Patent 2,692,822 (1955); *Chem. Abstr.*, **49**, 2014 (1955).

[6] H. Gysin and E. Knüsli, German Patent 1,035,398 (1960); *Chem. Abstr.*, **54**, 25543 (1960).

[7] U. Burckhardt and M. Zimmermann, German Patent 2,209.430 (1972); *Chem. Abstr.* **77**, 164744 (1972).

[8] J. M. Smith, Jr., U. S. Patent 2,512,180 (1950); *Chem. Abstr.*, **44**, 15946 (1950).

[9] J. H. Blumenthal, U. S. Patent 2,874,162 (1959); *Chem. Abstr*, **53**, 123116 (1959).

[10] J. L. Neumeyer and J. G. Cannon, *J. Pharm. Sci.*, **51**, 804 (1962).

[11] J. M. Smith, Jr., H. W. Stewart, B. Roth and E. M. Northey, *J. Am. Chem. Soc.*, **70**, 3997 (1948).