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SOME REACTIONS OF 3-HALOGENOCINNOLINES CATALYSED BY PALLADIUM COMPOUNDS

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Abstract—3-Bromo- or 3-iodo-cinnoline (and 4-substituted analogues) are condensed with terminal alkynes in the presence of Pd and Cu compounds as catalysts to give the 3-alkynyl-derivatives. When 4-chloro- or 4-phenoxy-compounds are used, the products react with amines, in the presence of copper(I) iodide, to form pyrrolo[3,2-c]cinnolines and with hydrazines to give either the same ring system or a pyrazolo[4,3-c]cinnoline. Hydrolysis of 3-alkynyl-4-phenoxycinnoline to 3-alkynyl-4(1H)-cinnolinone, followed by cyclisation, yields the furo[3,2-c]cinnoline. Attempts to condense 3-halogenocinnolines with alkenes gave variable results: 3-phenyl ethenyl- and 3(2-pyridylethenyl)-4-(1H)-cinnolinones were obtained but 3-bromocinnoline gave the 3,3'-bicinnolinyl. Action of palladium acetate in the presence of ethyl acrylate converted 3-bromo-4-phenoxycinnoline into benzofuro[3,2-c]cinnoline and 3-bromo-4-phenylaminocinnoline into indolo[3,2-c]cinnoline.

The objective of this work was to apply reactions catalysed by Pd compounds to 3-halogeno-4-substituted cinnolines as a route to tri- and tetra-cyclic compounds with a ring system fused at the 3,4-positions of the cinnoline ring.

Sonogashira *et al.*[1] have developed a valuable synthesis of arylacetylenes by reaction of aryl or pyridyl halides with terminal alkynes in the presence of catalytic amounts of a Pd complex and of copper(I) iodide in diethylamine under very mild conditions. Application of this method to 3-bromo- and to 3-iodo-cinnoline in condensation with phenylethyne gave 3-phenylethynylcinnoline (36 and 45% respectively) but 3-chlorocinnoline did not react (contrast chloroquinoxalines[2]). 3-Bromo-4-chlorocinnoline reacted with phenylethyne under similar conditions to give 4-diethylamino-3-phenylethynylcinnoline (**1a**) and piperidine (in 2-butanone) yielded the 4-piperidino-compound. When triethylamine was used as base and solvent, however, 4-chloro-3-phenylethynylcinnoline (**1b**) was obtained. The 4-chloro-substituent in cinnolines is highly reactive in nucleophilic displacement reactions[3] and its unreactivity in Sonogashira's reaction also contrasts with the replacement of both halogens of 2,3-dichloroquinoxaline which readily gives the dialkynyl derivative.[2]

Condensation of 3-bromo- and 3-iodo-4-phenoxycinnoline with phenylethyne and catalysts in triethylamine-hexamethylphosphoramide gave 4-phenoxy-3-phenylethynylcinnoline (**1c**; 28 and 35%) but again the 3-chloro-analogue did not react. These results correspond to those for the parent 3-halogenocinnolines showing that the steric effect of the large adjacent group plays little part in the reaction. Similar observations were made by Heck *et al.* in a study of arylation of methyl acrylate by substituted bromobenzenes.[4]

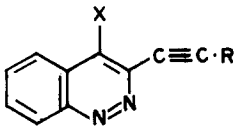
4-Chloro-, 4-diethylamino- and 4-phenoxy-3-phenylethynylcinnoline each reacted with ethanolic hydrazine to form 3-benzyl-1H-pyrazolo[4,3-c]cinnoline (**2a**). The absence of a C≡C band in the IR and Raman spectra showed that cyclisation had occurred and this 5-membered ring structure was indicated by the ^{1}H NMR band at δ 4.6 (CH_2) and by a major peak at *m/e* 91 (34%, CH_2Ph) in the mass spectrum. 4-Chloro-3-phenylethynylcinnoline condensed similarly with methylhydrazine to give 1-methyl-3-benzyl-1H-pyrazolo[4,3-c]cinnoline (**2b**) but with phenylhydrazine it yielded 1-phenylamino-2-phenyl-1H-pyrrolo[3,2-c]cinnoline (**3a**). The mass spectrum of this product showed the base peak at *m/e* 245, corresponding to the parent compound (**3b**) and a peak at *m/e* 93 (66%) corresponding to aniline. The formulation as **3a** is also in accord with the work of Tieckelmann who showed that arylhydrazines react with heteroaryl halides to form N,N'-disubstituted hydrazines.[5]

Fusion of 4-phenoxy-3-phenylethynylcinnoline with ammonium acetate[6] yielded 2-phenylpyrrolo[3,2-c]cinnoline (**3b**). Treatment of the phenoxy-compound with ethanolic methylamine gave 4-methylamino-3-phenylethynylcinnoline (**1d**), the IR spectrum of which showed the C≡C (ν_{max} 2200 cm^{-1}) and NH groups (3230 cm^{-1}). Ethylamine gave the 4-ethylamino-analogue (**1e**). Both these 4-alkylamino-3-phenylethynylcinnolines were cyclised by heating with copper(I) iodide in NN-dimethylformamide[7] to give the pyrrolocinnolines (**3c** and **3d**). When 4-phenoxy-3-phenylethynylcinnoline was heated with *o*-phenylenediamine in toluene, 1-(2-aminophenyl)-2-phenylpyrrolo[3,2-c]cinnoline (**3e**) was obtained. The assignment of this structure was based on the similarity of the UV spectrum to that of the isomeric **3a**, the presence of an NH_2 group (ν_{max} 3500, 3400 cm^{-1}) and the absence of a CH_2 group peak in the ^{1}H NMR spectrum.

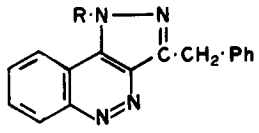
Hydrolysis of 4-phenoxy-3-phenylethynylcinnoline with dilute acid gave 3-phenylethynyl-4-(1H)-cinnolinone. When this product was heated with copper(I) iodide in pyridine,[7] 2-phenylfuro[3,2-c]cinnoline (**4a**) was obtained. This was also prepared directly by heating 3-iodo-4(1H)-cinnolinone with copper(I) phenylethynide in pyridine.[7] Fusion of the furo-compound with ammonium acetate again gave 2-phenyl-1H-pyrrolo[3,2-c]cinnoline (**3b**; 50%).

It has been shown[8] that use of 2-methylbut-3-yn-2-ol in Sonogashira's reaction with heterocyclic halides, followed by base-catalysed degradation of the alkynol to eliminate acetone, gives ethynylheteroarene in good yield. Thus 3-bromo-4-phenoxycinnoline was converted into 3-ethynyl-4-phenoxy cinnoline (**1f**) which was hydrolysed to 3-ethynyl-4(1H)-cinnolinone. Cyclisation with copper(I) iodide then gave furo[3,2-c]cinnoline (**4b**) and the phenoxy-compound also reacted with hydrazines to form pyrazolocinnolines (ring system as 2).

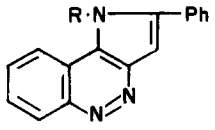
Condensation of 3-bromo-1-methyl-4(1H)cinnolinone with phenylethyne yielded 3-phenylethynyl-1-methyl-

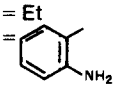


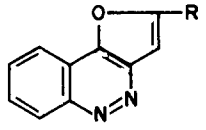
1a: X = NEt_2 R = Ph
1b: X = Cl R = Ph
1c: X = OPh R = Ph
1d: X = NHMe R = Ph
1e: X = NHEt R = Ph
1f: X = OPh R = H



2a: R = H
2b: R = Me



3a: R = NHPh
3b: R = H
3c: R = Me
3d: R = Et
3e: R = 



4a: R = Ph
4b: R = H

4(1H)-cinnolinone but 3-iodo-4(1H)-cinnolinone was cyclised, presumably by copper(I) iodide even under the mild conditions of Sonogashira's reaction, to form 2-phenylfuro[3,2-c]cinnoline (**4a**). Other 2-substituted furocinnolines were also prepared from terminal alkynes.

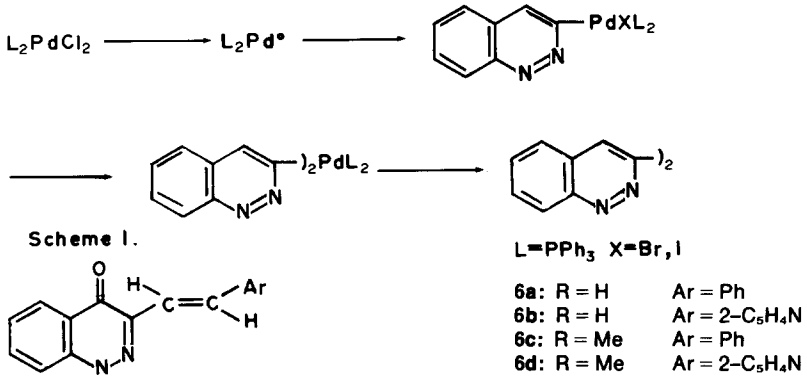
Many reports have described Pd catalysed condensation reactions of aromatic halides with alkenes and unsaturated esters and ketones.[9] The use of 3-halogenocinnolines in such reactions was therefore examined by heating the reactants in acetonitrile and triethylamine with bis(triphenylphosphine)palladium(II) dichloride at 150° in an autoclave for 5 hr. 3-Bromo- and 3-iodocinnoline did not react with styrene under these conditions but a coupling reaction occurred forming the novel 3,3'-bicinnolinyl in high yield and similar results were obtained when the styrene was omitted. The reaction Scheme 1 is suggested to account for bicinnolinyl formation.

Condensation of 3-iodo-4(1H)-cinnolinone with styrene, and with 3-ethenylpyridine, gave the alkenylcinnolinone, **6a** and **6b** respectively. The *trans*-configuration of the double bond was shown by the IR band at about 970 cm^{-1}, and by a multiplet at δ 7.94 with coupling constant J = 16.5 Hz in the ^1H NMR spectra, and is consistent with Heck's results.[10] Similarly 3-bromo-1-methyl-4(1H)-cinnolinone with styrene and 2-ethenyl pyridine yielded the alkenylcinnolinones **6c** and **6d**, showing similar spectra. The formation of 1,2-disubstituted ethene was further confirmed by catalytic hydrogenation of **6c** to form 1-methyl-3-(2phenylethyl)-4-(1H)-cinnolinone which was also obtained by reduction of 1-methyl-3-phenylethynyl-4-(1H)-cinnolinone.

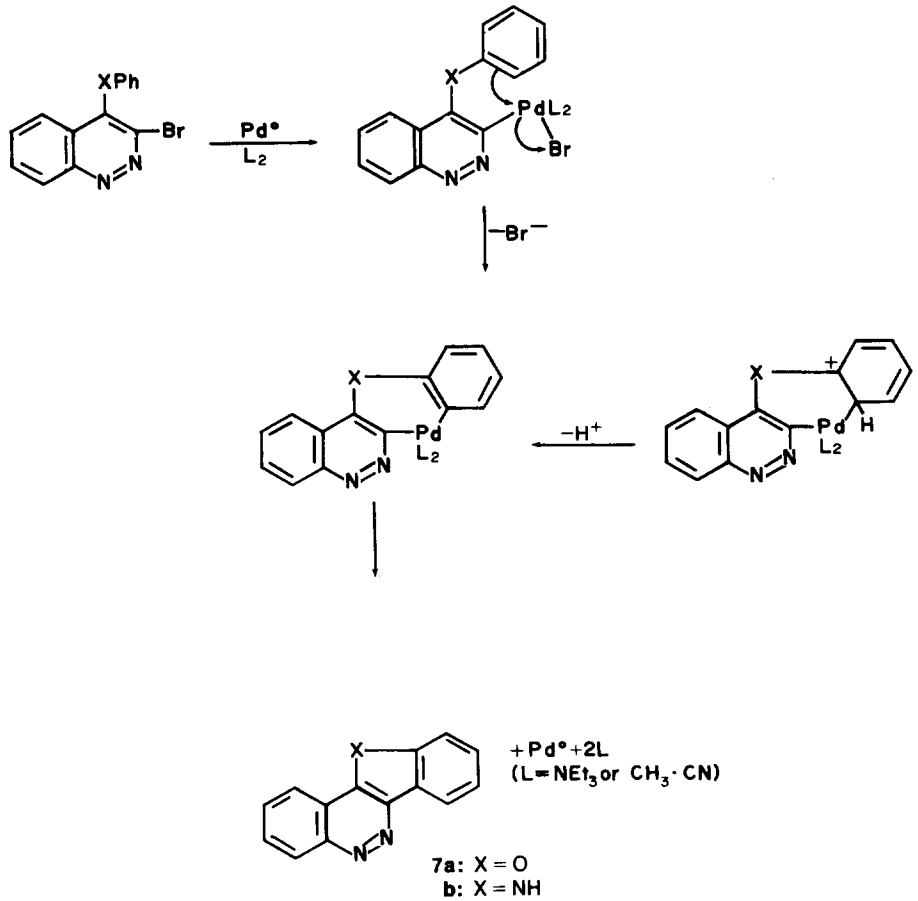
When 3-bromo-4-phenoxycinnoline was heated with styrene under the same conditions, no condensation or coupling occurred. In view of the possible steric effects of the large 4-phenoxy-group and the triphenylphosphine ligands (see Ref. 10), the experiment was repeated using palladium acetate as catalyst and 4-phenoxy-3-phenylethenylcinnoline was isolated in 31% yield. 2-Ethenylpyridine failed to react when either catalyst was used. Treatment of 3-bromo-4-phenoxycinnoline with ethyl acrylate using palladium acetate catalyst did not effect condensation but intramolecular dehydrobromination occurred to give benzofuro[3,2-c]cinnoline (**7a**) in 19% yield. The same product was obtained by action of palladium acetate on 3-bromo-4-(*o*-bromophenoxy)cinnoline.

Akermark *et al.*[11] have obtained dibenzofuran from diphenyl ether by heating with palladium acetate in acetic acid but the acid-catalysed dehydrogenation reaction requires at least stoichiometric amounts of Pd salt whereas only catalytic amounts were used in the present experiments. Shiotani and Itatani[12] obtained dibenzofuran from diphenyl ether under neutral conditions and the reaction could be made catalytic in Pd when the reactants were heated in an atmosphere enriched in oxygen.

When 3-bromo-4-phenoxycinnoline was heated with palladium acetate, triethylamine and acetonitrile in the absence of ethyl acrylate, no benzofurocinnoline was isolated. Since the alkene present in the Heck arylation reaction[9] is believed to generate the catalytic Pd(O) species from Pd(II) compound, the first step in the cyclisation of 3-bromo-4-phenoxycinnoline is probably the same. Attempted cyclisation of 4-phenoxycinnoline by palladium acetate in acetic acid[11] gave no benzofurocinnoline so that direct palladation, involved in the cyclisation of diphenyl ether,[11] does not occur with the highly deactivated diazine ring. These observations suggest the reaction sequence of Scheme 2 to account for



Scheme 1.



Scheme 2.

the formation of benzofurocinnoline, palladation being followed by electrophilic attack on the phenoxy-ring and the elimination of Pd(O).

Reaction of 3-brom-4-phenylaminocinnoline with palladium acetate in the presence of ethyl acrylate similarly gave indolo[3,2-c]cinnoline (**7b**) in 55% yield, providing a simple route to this ring system. Only a small amount of impure product was obtained when ethyl acrylate was omitted, again suggesting a reaction sequence as in Scheme 2.

EXPERIMENTAL

M.ps (capillary) are uncorrected. NMR spectra were determined at 60 MHz on a Perkin Elmer R12B spectrometer in DMSO with TMS as internal standard. Mass spectra were determined on an AEI MS-902 spectrometer. Petrol refers to light petroleum, fraction b.p. 60–80°.

3-Iodo-4(1H)-cinnolinone. Iodine monochloride (3 ml, molten) was added dropwise to 4(1H)-cinnolinone (4.38 g) and anhyd. NaOAc (3 g) in AcOH (75 ml) at 100°. The cooled mixture was poured into 0.5M Na_2SO_3 to give *3-iodo-4(1H)-cinnolinone* (7.8 g; 95%), m.p. 294–296°, from 2-methoxyethanol (Found: C, 35.2; H. 1.7; N, 10.2. $C_8H_5IN_2O$ requires: 35.3; H, 1.8; N, 10.3%).

4-Chloro-3-iodocinnoline. 3-Iodo-4(1H)-cinnolinone (4 g) and $POCl_3$ (100 ml) were stirred and heated (bath 140°) for 10 min. Evaporation, addition of ice, neutralisation with Na_2CO_3, and isolation with EtOAc gave *product* (3.6 g; 84%), m.p. 165–166°, from toluene (Found: C, 33.2; H, 1.2; I, 43.3; N, 9.6. $C_8H_6ClIN_2$ requires: C, 33.0; H, 1.4; I, 43.7; N, 9.6%).

3-Iodocinnoline. Toluene-*p*-sulphonylhydrazine (3 g) was added to a soln of 4-chloro-3-iodocinnoline (2.2 g) in $CHCl_3$ (75 ml).[13] After 1 week at room temp., the red ppt (3.3 g) was collected and added to 5M Na_2CO_3 (250 ml) at 95° and heated under reflux for 1.5 hr. Isolation with $CHCl_3$, and crystallisation from petrol gave 3-iodocinnoline (1.4 g; 72%), yellow, m.p. 102–103° (Found: C, 37.8; H, 1.8; N, 11.0%; M^+, 256. $C_8H_5IN_2$ requires: C, 37.5; H, 2.0; N, 10.9%; M, 256), λ_{max} 235 nm (ϵ, 54,000).

3-Phenylethynylcinnoline. Copper(I) iodide (10 mg) was added to a soln of 3-iodocinnoline (0.5 g), phenylethyne (0.25 g) and bis(triphenylphosphine)palladium(II)dichloride (10 mg) in diethylamine (15 ml) under N_2.[1] The mixture was stirred for 4 hr, evaporated, and treated with water. Isolation with ether and crystallisation from petrol gave *3-phenylethynylcinnoline* (0.2 g; 45%), yellow, m.p. 127–128° (Found: C, 83.2; H, 4.3; N, 12.0%; M^+, 230. $C_{16}H_{10}N_2$ requires: C, 83.4; H, 4.4; N, 12.2%; M, 230); λ_{max} 216, 258, 269, 333 and 351 nm (ϵ 31,000, 34,500, 42,000, 26,000 and 29,000); ν_{max} 2200 cm^{-1} (C≡C).

Condensations of 3-bromo-4-chlorocinnoline with phenylethyne

Condensation as above[1] using diethylamine yielded *4-diethylamino-3-phenylethynylcinnoline* (37%), yellow prisms from EtOH, m.p. 116–117° (Found: C, 79.4; H, 6.3; N, 13.9. $C_{20}H_{19}N_3$ requires: C, 79.7; H, 6.3; N, 13.9%). Similarly piperidine gave *3-phenylethynyl-4-(N-piperidinyl)cinnoline* (64%), m.p. 165–166°, from EtOH (Found: C, 80.7; H, 6.2; N, 13.2. $C_{21}H_{19}N_3$ requires: C, 80.5; H, 6.1; N, 13.4%). When triethylamine was used as base, *4-chloro-3-phenylethynylcinnoline* (29%), m.p. 135–136°, from EtOH, was obtained (Found: C, 72.7; H, 3.4; Cl, 13.3; N, 10.6. $C_{16}H_{19}ClN_2$ requires: C, 72.6; H, 3.4; Cl, 13.4; N, 10.6%).

Reactions of 4-chloro-3-phenylethynylcinnoline with hydrazines

The chloro-compound (0.5 g) in EtOH (10 ml) and hydrazine

(0.3 g, anhyd.) were heated under reflux for 1 hr. The solid was collected, washed with water, and crystallised from EtOH to give 3-*benzyl*-1H-*pyrazolo*[4,3-*c*]*cinnoline* (**2a**) (0.1 g; 20%), m.p. 291–293° (Found: C, 73.2; H, 4.6; N, 20.9. $C_{16}H_{12}N_4$ requires: C, 73.8; H, 4.6; N, 21.5%); ν_{max} 2750 cm^{-1} (br NH); δ 4.62 (2H, s, CH_2) and 7.2–8.8 (9H, m, ArH); *m/e* 261 (100%, $M^+ + 1$), 260 (80%, M^+) and 91 (34%, CH_2Ph). 4-Diethylamino-3-phenylethynylcinnoline reacted similarly giving the product (28%).

The chloro-compound (250 mg) and methylhydrazine (100 mg) in EtOH (5 ml) were left at room temp. overnight. Filtration and recrystallisation from EtOH gave 3-*benzyl*-1-*methyl*-1H-*pyrazolo*[4,3-*c*]*cinnoline* (**2b**) (100 mg) (39%), m.p. 179–180° (Found: C, 74.5; H, 4.8; N, 20.5. $C_{17}H_{14}N_4$ requires: C, 74.4; H, 5.1; N, 20.4%); δ 4.44 (3H, s, N–Me), 4.58 (2H, s, CH_2) and 7.2–8.7 (9H, m, ArH); *m/e* 274 (88%, M^+) and 91 (19%, CH_2Ph).

Phenylhydrazine (220 mg) and the chloro-compound (260 mg) in EtOH (10 ml) were heated under reflux for 15 min. Evaporation, trituration with water, and crystallisation from MeOH gave 1-*phenylamino*-2-*phenyl*-1H-*pyrrolo*[3,2-*c*]*cinnoline* (**3a**) as the hydrochloride (100 mg, 30%), m.p. 251–252° (Found: C, 70.4; H, 4.3; Cl, 9.8; N, 14.7. $C_{22}H_{17}ClN_4$ requires: C, 70.8; H, 4.6; Cl, 9.5; N, 15.0%); δ 6.4–8.8 (14H, m, ArH), 7.88 superimposed (1H, s, 3-CH) and 10.74 (1H, s, NH); *m/e* 336 (46% M^+), 245 (100%), and 93 (66%, $PhNH_2$).

Condensation reactions with terminal alkynes

The following conditions were used in subsequent reactions: phenylethyne (1 g) and **2g** were dissolved in a mixture of hexamethylphosphoramide (10 ml) and triethylamine (50 ml) under N_2. After addition of bis(triphenylphosphine)palladium dichloride (100 mg) and copper(I) iodide (100 mg), the mixture was stirred for 6 hr and evaporated. Addition of water and isolation with benzene gave 4-*phenoxy*-3-*phenylethynylcinnoline* (**1c**) (28%), m.p. 152–153°, from benzene–petrol (Found: C, 82.0; H, 4.4; N, 8.7. $C_{22}H_{14}N_2O$ requires: C, 82.0; H, 4.4; N, 8.7%). 3-Iodo-4-phenoxycinnoline similarly gave product in 35% yield.

3-*Phenylethynyl*-4(1H)-*cinnolinone*. 4-Phenoxy-3-phenylethynylcinnoline (250 mg) and 2M HCl (1.5 ml) in EtOH (6 ml) were heated under reflux for 10 min and poured into water. Filtration and crystallisation from EtOH gave the *cinnolinone* (100 mg), m.p. 180–181° (Found: C, 77.7; H, 4.0; N, 11.4. $C_{16}H_{10}N_2O$ requires: C, 78.1; H, 4.1; N, 11.4%); δ 3.4 (1H, br s, NH exchanges with D_2O) and 7.4–8.3 (9H, m, ArH). This compound (0.5 g) and copper(I) iodide (0.1 g) in pyridine (10 ml) were heated (bath 110°) under N_2 for 1 hr. Evaporation, addition of aqueous ammonia (10 ml; d 0.88) and isolation with ether gave 2-*phenylfuro*[3,2-*c*]*cinnoline* (**4a**) (0.4 g), pale yellow, m.p. 161–163° (Found: C, 78.0; H, 3.9; N, 11.3%; M^+, 246. $C_{16}H_{10}N_2O$ requires: C, 78.0; H, 4.1; N, 11.4%; M, 246).

Preparation of 2-*phenylfuro*[3,2-*c*]*cinnoline*. A mixture of copper(I) phenylethynide (1.65 g), 3-iodo-4(1H)-cinnolinone (2.72 g), and dry pyridine (60 ml) was refluxed (bath 120°) under N_2 for 9 hr. Pyridine was removed under reduced pressure, aqueous ammonia (60 ml; d 0.88) was added, and the mixture was extracted with ether. The ether extract was washed with water, dried ($MgSO_4$), and evaporated to give **4a** (2.0 g; 81%), m.p. and mixed m.p. 161–163° from EtOAc.

Reactions of 4-*phenoxy*-3-*phenylethynylcinnoline*

(a) *With ammonium acetate*. The cinnoline (450 mg) and ammonium acetate (3 g) were powdered, mixed, and heated slowly to 160°. The mixture was stirred at 160° for 20 min, cooled, and triturated with water. Filtration and crystallisation from toluene gave 2-*phenyl*-1H-*pyrrolo*[3,2-*c*]*cinnoline* (**3b**) (180 mg; 53%), m.p. 332–335° (Found: C, 78.4; H, 4.3; N, 17.0%; M^+, 245. $C_{16}H_{11}N_3$ requires: C, 78.4; H, 4.5; N, 17.1%; M, 245). The furocinnoline on similar treatment gave the same product (50%).

(b) *With methylamine*. The cinnoline (300 mg) and ethanolic methylamine (10 ml; 33%) were heated under reflux for 10 min. Evaporation, washing with water, and crystallisation from EtOH gave 4-*methylamino*-3-*phenylethynylcinnoline* **1d**; (200 mg; 83%), m.p. 165–166° (Found: C, 78.7; H, 4.8; N, 16.2%; M^+, 259. $C_{17}H_{13}N_3$ requires: C, 78.7; H, 5.0; N, 16.2%, M, 259); ν_{max} 2200 cm^{-1} (C≡C); δ 3.55 (3H, d, N–Me) and 7.3–8.5 (9H, m, ArH). This 0.4 g in DMF (10 ml) containing copper(I) iodide (0.3 g) was stirred at 120° under N_2 for 8 hr. Evaporation, addition of aqueous ammonia (50 ml; d 0.88) and isolation with chloroform gave 1-*methyl*-2-*phenyl*-1H-*pyrrolo*[3,2-*c*]*cinnoline* (**3c**) (0.3 g; 75%), m.p. 133–134°, resolidifying and then melting at 145°, from ethyl acetate–petrol (Found: C, 78.5; H, 5.1; N, 16.0%; M^+, 259. $C_{17}H_{13}N_3$ requires: C, 78.8; H, 5.0; N, 16.2%; M, 259); δ 4.05 (3H, s, N–Me), 7.15 (1H, s, 3-CH), and 7.45–8.7 (9H, m, ArH).

(c) *With ethylamine*. This reaction similarly gave 4-*ethylamino*-3-*phenylethynylcinnoline* (59%; **1e**), m.p. 168–169° from EtOH (Found: C, 78.9; H, 5.7; N, 15.4%; M^+, 273. $C_{18}H_{15}N_3$ requires: C, 79.1; H, 5.5; N, 15.4%; M, 273) which cyclised to form 1-*ethyl*-2-*phenyl*-1H-*pyrrolo*[3,2-*c*]*cinnoline* (**3d**) (80%), m.p. 131–132° from toluene (Found: C, 79.1; H, 5.3; N, 15.4%; M^+, 273); δ 1.3 (3H, t, Me), 3.3 (2H, q, CH_2), 7.25 (1H, s, 3-CH) and 7.4–8.7 (9H, m, ArH).

(d) *With* o-*phenylene diamine*. The diamine (100 mg) and the cinnoline (250 mg) were dissolved in toluene and heated under reflux for 3 hr. Evaporation and crystallisation from EtOH gave 1-(o-*aminophenyl*)-2-*phenyl*-1H-*pyrrolo*[3,2-*c*]*cinnoline* (**3e**; 140 mg; 54%), orange, m.p. 248–250° (Found: C, 78.7; H, 4.6; N, 16.7%; M^+, 336. $C_{22}H_{16}N_4$ requires: C, 78.6; H, 4.8; N, 16.7%; M, 336); ν_{max} 3500 and 3400 cm^{-1} (NH_2); δ 5.2 (2H, s, NH_2 exchanges with D_2O) and 7.6 (1H, s, 3-CH) superimposed on 6.4–8.6 (13H, m, ArH).

Reactions of 3-*ethynyl*-4-*phenoxycinnoline*

(a) *Hydrolysis*. The cinnoline[8] was hydrolysed with EtOH–HCl as above to obtain 3-*ethynyl*-4(1H)-*cinnolinone* (72%), m.p. 192–193° from aqueous EtOH (Found: C, 70.4; H, 3.6; N, 16.1. $C_{10}H_6N_2O$ requires: C, 70.6; H, 3.5; N, 16.5%). This with copper(I) salt as before gave *furo*[3,2-*c*]*cinnoline* (**4b**; 30%), m.p. 137–138° from petrol (Found: C, 70.7; H, 3.5; N, 16.5%).

(b) *With hydrazine*. 3-Ethynyl-4-phenoxycinnoline (300 mg) and anhyd. hydrazine (0.3 ml) in 2-propanol (1.5 ml) were heated under reflux for 10 min. Filtration and recrystallisation from 2-propanol gave 3-methyl-1H-pyrazolo[4,3-c]cinnoline (67%), m.p. 342–343° (lit.[14] 342°).

(c) *With methylhydrazine*. A soln of the cinnoline (100 mg) and methyl hydrazine (100 mg) in EtOH (1.5 ml) was boiled under reflux for 10 min. Cooling, filtration, and crystallisation from EtOH gave 1,3-*dimethyl*-1H-*pyrazolo*[4,3-*c*]*cinnoline* (25 mg; 31%), m.p. 203–204° (Found: C, 66.5; H, 5.0; N, 28.6. $C_{11}H_{10}N_4$ requires: C, 66.7; H, 5.1; N, 28.3%); δ 2.77 (3H, s, C–Me), 4.39 (3H, s, N–Me), and 7.8–8.8 (4H, m, ArH).

1-*Methyl*-3-*phenylethynyl*-4(1H)-*cinnolinone*. Condensation of phenylethyne with 3-bromo-1-methyl-4(1H)-cinnolinone gave 1-*methyl*-3-*phenylethynyl*-4(1H)-*cinnolinone* (15%), m.p. 156–157° from EtOH (Found: C, 78.6; H, 4.6; N, 10.6%; M^+, 260. $C_{17}H_{12}N_2O$ requires: C, 78.4; H, 4.6; N, 10.8%; M, 260); δ 4.14 (3H, s, Me) and 7.3–8.2 (9H, m, ArH). This (0.52 g) in EtOH (100 ml) was hydrogenated in presence of Pd/C (0.1 g; 10%), reduction being complete in 10 min. Filtration, evaporation, and crystallisation from EtOH afforded 1-*methyl*-3-*phenyl ethyl*-4(1H)-*cinnolinone* (0.30 g; 57%), m.p. 111–112° (Found: C, 77.6; H, 6.1; N, 10.6. $C_{17}H_{16}N_2O$ requires: C, 77.3; H, 6.1; N, 10.6%); *m/e* 264 (100% M^+), 249 (30%, M–Me), 173 (90% M–$PhCH_2CH_2$), 105 (32%, $PhCH_2CH_2$) and 91 (12%, $PhCH_2$).

Condensation of 3-*iodo*-4(1H)-*cinnolinone with alkynes*

The iodo-compound (1.36 g) and phenylethyne (1.1 g) were condensed as above. The crude product was purified by chromatography on alumina using toluene to give 2-phenylfuro[3,2-c]cinnoline (0.6 g; 49%), m.p. and mixed m.p. 158–160°. The following compounds were prepared similarly and purified by crystallisations: 2-(1-*hydroxymethyl*)*furo*[3,2-c]*cinnoline* (33%), m.p. 152–153° (Found: C, 68.2; H, 5.2; N, 12.3. $C_{13}H_{12}N_2O_2$ requires: C, 68.4; H, 5.3; N, 12.3%); 2-(3-*quinolyl*)*furo*[3,2-*c*]*cinnoline* (57%), m.p. 272–274% from 2-methoxyethanol (Found: C, 76.7; H, 3.4; N, 14.0. $C_{19}H_{11}N_3O$ requires: C, 76.8; H, 3.7; N, 14.1%); and 2-(4-*isoquinolyl*)*furo*[3,2-c]*cinnoline* (59%), m.p. 246–247° from 2-methoxyethanol (Found: C, 76.7; H, 3.5; N, 14.0%).

Preparation of 3,3'-*bicinnolyl*. 3-Bromocinnoline (500 mg), acetonitrile (2 ml), triethylamine (250 mg) and bis(triphenylphosphine)palladium(II) dichloride (10 mg) were heated at 150° in an autoclave for 5 hr. Evaporation and crystallisation from 2-methoxyethanol gave 3,3'-*bicinnolyl* (250 mg, 81%), m.p. 326–327°

(Found: C, 74.9; H, 3.9; N, 21.7. $C_{16}H_{10}N_4$ requires: C, 74.4; H, 3.9; N, 21.7%); *m/e* 258 (100%, M·), and 202 (100%, M–$2N_2$). 3-Iodocinnoline gave the same product (77%).

Reaction of 3-iodo-4(1H)-cinnolinone with styrene

A mixture of the cinnolinone (1.36 g), styrene (0.52 g), acetonitrile (4 ml), triethylamine (0.52 g), and bis(triphenylphosphine)palladiumdichloride (10 mg) was heated in an autoclave at 150° for 5 hr. Evaporation and crystallisation from 2-methoxyethanol gave E-3-*phenylethenyl*-4-(1H)-*cinnolinone* (**6a**; 0.65 g; 52%), m.p. 295° (Found: C, 77.5; H, 4.9; N, 11.2. $C_{16}H_{12}N_2O$ requires: C, 77.4; H, 4.9; N, 11.3%); ν_{max} 970 cm^{-1} (*trans* CH=CH); δ 7.3–8.2 (9H, m, ArH) with superimposed doublet at δ 7.94 (2H, *trans* CH=CH, J 16.5 Hz), and 13.2 (1H, br s, NH exchanges with D_2O).

Similarly 3-bromo-1-methyl-4(1H)-cinnolinone gave E-1-*methyl*-3-*phenylethenyl*-4(1H)-*cinnolinone* (**6c**; 69%), m.p. 142–144° from toluene–petrol (Found: C, 77.7; H, 5.5; N, 10.8. $C_{17}H_{14}N_2O$ requires: C, 77.8; H, 5.5; N, 10.8%); ν_{max} 972 cm^{-1} (*trans* CH=CH); δ 3.9 (3H, s, N–Me), 7.93 (2H, d, J 16.5 Hz, *trans* CH=CH) superimposed on δ 7.0–8.2 (9H, m, ArH). 3-Iodo-4(1H)-cinnolinone and 2-ethenylpyridine similarly gave E-3-(2-*pyridylethenyl*)-4(1H)-*cinnolinone* (**6b**; 4%), m.p. 283–284° from 2-methoxyethanol (Found: C, 71.8; H, 4.5; N, 16.6. $C_{15}H_{11}N_3O$ requires: C, 72.3; H, 4.4; N, 16.9%); ν_{max} 985 cm^{-1} (*trans* CH=CH); and 3-bromo-1-methyl-4(1H)-cinnolinone yielded E-1-*methyl*-3-(2-*pyridylethenyl*)-4(1H)-*cinnolinone* (60%), m.p. 157–158° from EtOH (Found: C, 73.1; H, 5.1; N, 16.0. $C_{16}H_{13}N_3O$ requires: C, 73.0; H, 5.0; N, 16.0%); ν_{max} 980 cm^{-1} (*trans* CH=CH).

Catalytic hydrogenation of 1methyl - 3 - phenylethenyl - 4(1H) - cinnolinone. The cinnolinone (0.52 g) was dissolved in EtOH (100 ml) and hydrogenated in the presence of Pd/C (0.1 g; 10%). When absorption ceased, the solution was filtered and evaporated. Crystallisation of the residue from EtOH gave 1 - methyl - 3 - (2 - phenylethyl) - 4(1H) - cinnolinone (0.41 g; 80%), m.p. and mixed m.p. 111–112°.

E-4-*Phenoxy*-3-*phenylethenylcinnoline.* 3-Bromo-4-phenoxycinnoline (1.5 g) and styrene (0.52 g) were condensed as in the preceding examples but palladium(II) acetate (20 mg) was used as catalyst. Evaporation and chromatography on alumina in toluene gave the *product* (0.50 g; 31%), m.p. 185–186° from EtOH (Found: C, 81.4; H, 4.8; N, 8.6. $C_{22}H_{16}N_2O$ requires: C, 81.5; H, 5.0; N, 8.6%); ν_{max} 975 cm^{-1} (*trans* CH=CH).

Benzofuro[3,2-c]*cinnoline.* A mixture of 3-bromo-4-phenoxycinnoline (1.5 g), ethyl acrylate (0.52 g), acetonitrile (4 ml), triethyamine (0.52 g), and palladium(II) acetate (20 mg) was heated under N_2 in an autoclave at 150° for 5 hr. Evaporation and chromatography on alumina in toluene gave 3-bromo-4-phenoxycinnoline (0.5 g, 33% recovery) and *benzofuro*[3,2-c]*cinnoline* (**7**; 0.21 g, 19% or 29% on bromo-compound consumed), m.p. 192–193° (Found: C, 76.4; H, 3.7; N, 12.7. $C_{14}H_8N_2O$ requires C, 76.4; H, 3.7; N, 12.7%); *m/e* 220 (100% M·) and 192 (M–N_2).

3-*Bromo*-4-(o-*bromophenoxy*)*cinnoline.* 3-Bromo-4-chlorocinnoline (1.2 g) was added to KOH (0.35 g) in *o*-bromophenol (7 g) and the mixture was heated on a steam-bath for 2 hr. Addition of 2M NaOH and isolation with toluene gave the *product* (1.6 g; 84%), m.p. 199–200° (Found: C, 44.4; H, 2.0; Br, 42.0; N, 7.4. $C_{14}H_8Br_2N_2O$ requires: C, 44.2; H, 2.1; Br, 42.1; N, 7.4%). Treatment with palladium acetate as in the previous experiment (ethyl acrylate omitted) again gave benzofuro[3,2-c]cinnoline (23%), m.p. and mixed m.p. 192–193°.

3-*Bromo*-4-*phenylaminocinnoline.* 3-Bromo-4-phenoxycinnoline (1.8 g) and redistilled aniline (0.9 g) were heated at 175° for 20 min and cooled. Crystallisation from EtOH yielded the *amine* (1.5 g), m.p. 194–196° (Found: C, 56.5; H, 3.2; N, 14.2; Br, 26.9. $C_{14}H_{10}BrN_3$ requires: C, 56.0; H, 3.4; N, 14.0; Br, 26.6%).

Indolo[3,2-c]*cinnoline.* The amine (0.5 g), acetonitrile (3 ml), triethylamine (0.25 g), and palladium acetate (20 mg) were heated in an autoclave at 150° for 5 hr. Trituration with water and crystallisation from EtOH gave *indolo*[3,2-c]*cinnoline* (**8**; 0.2 g; 55%), m.p. >360° (Found: C, 76.3; H, 4.0; N, 18.81. $C_{14}H_9N_3$ requires: C, 76.7; H, 4.1; N, 19.2%); *m/e* 219 (100% M·), 191 (18%, M–N_2) and 190 (50%).

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