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Synthesis of 4-haloquinolines and their fused polycyclic derivatives

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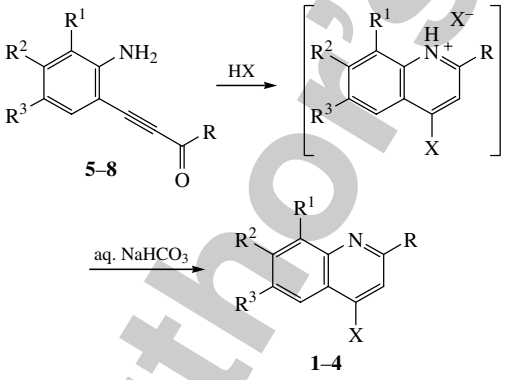
A general method for the synthesis of 4-chloro- or 4-bromo-substituted quinolines and quinoline moieties of polycyclic compounds includes the addition of hydrogen halides to *vic*-amino(3-oxoalk-1-ynyl)arenes under mild conditions followed by the intramolecular cyclization of the adducts.

A variety of biologically active compounds and materials contain a quinoline or quinoline-5,8-dione fragment, *e.g.* (20*S*)-camptothecin and its derivatives,[1] cleistopholine,[2] sampangin,[2,3] ascididemin and its analogues,[4] arylquinolines[5] and polymers incorporating them.[6] A general approach to polynuclear condensed heterocycles, which consists in the cyclization of functionalised acetylenic precursors, is intensively developed.[7] Previously we applied this approach to the synthesis of a 4-dialkylaminoquinoline moiety using *vic*-amino(3-oxoalk-1-ynyl)arenes as key precursors.[8] The method involved the addition of secondary amines to the triple bond of acetylenic ketones and the subsequent heterocyclization of the adducts in the presence of a mineral acid or base. Marinelli *et al*.[9] proposed rhodium-catalyzed tandem hydroarylation (hydrovinylation)–cyclization reactions for the preparation of arylated and arylvinylated quinolines. The above acetylenic building blocks and arylboronic acids or potassium aryltrifluoroborates and potassium arylvinyltrifluoroborates, respectively, were used as initial materials. Unfortunately, both methods allow one to obtain quinolines only with determinate substituent types in a pyridine ring, which cannot usually be replaced by other functional groups. Furthermore, the protection of functional groups in the acetylenic precursors, which are sensitive to nucleophiles, is a problem. The precursors and reaction intermediates can be unstable at elevated temperatures (up to 100 °C). Here we report a new synthesis of polycyclic compounds containing 4-haloquinoline and 4-haloquinoline-5,8-dione moieties on the basis of the above precursors. Alkyl ethynyl ketones add hydrogen halides to yield regioselectively corresponding β-halovinyl ketones.[10] *Z*-Isomers of the formed compounds can easily transform into *E*-isomers under mild conditions. We suggested that *vic*-amino(3-oxoalk-1-ynyl)arenes react with hydrogen halides in the same manner. If it is true, the addition is followed by acid-catalysed isomerization of *Z*-adducts into *E*-isomers and intramolecular cyclization of the latter to close a pyridine ring. This assumption was confirmed by the synthesis of 4-bromo-2-phenylquinoline **1** and a series of condensed polycyclic compounds **2a**,**b**, **3a**,**b** and **4a**,**b** containing a haloquinoline moiety (Table 1).†

Table 1 Synthesis of haloquinoline structures.



Substrate	R	R^1	R^2	R^3	X	Product	Yield (%)
5	Ph	H	H	H	Br	**1**	73
6	Pr^i	Cl	*ortho*-CO–C_6H_4–CO–		Cl	**2a**	77
6	Pr^i	Cl	*ortho*-CO–C_6H_4–CO–		Br	**2b**	70
7	Ph	*ortho*-CO–C_6H_4–CO–	H		Cl	**3a**	65
7	Ph	*ortho*-CO–C_6H_4–CO–	H		Br	**3b**	90
8	Bu^t	*ortho*-CO–C_6H_4–CO–	H		Cl	**4a**	82
8	Bu^t	*ortho*-CO–C_6H_4–CO–	H		Br	**4b**	69

† *General heterocyclization procedure*: a solution of an acetylenic precursor (1.0 mmol) in dry dioxane or $CHCl_3$ (15 ml) under Ar was mixed with a solution (4–5 ml) containing 2.5–3 equiv. of hydrogen halide in the above solvent and stirred at 20 °C for 5–6 h. After the neutralization of the hydrohalide formed, the product was isolated and purified in a usual way.

1: mp 90–91 °C (EtOH).[11]

2a: mp 194–195 °C (Et_2O). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.30 (d, 6H, Me, *J* 6.9 Hz), 3.35 (sept., 1H, CH, *J* 6.9 Hz), 7.64 (s, 1H, H^3), 7.75–7.90 (m, 2H, $H^{8,9}$), 8.25–8.40 (m, 2H, $H^{7,10}$), 9.18 (s, 1H, H^5). Found (%): C, 64.91; H, 3.67; Cl, 19.02. Calc. for $C_{20}H_{13}Cl_2NO_2$ (%): C, 64.88; H, 3.54; Cl, 19.15.

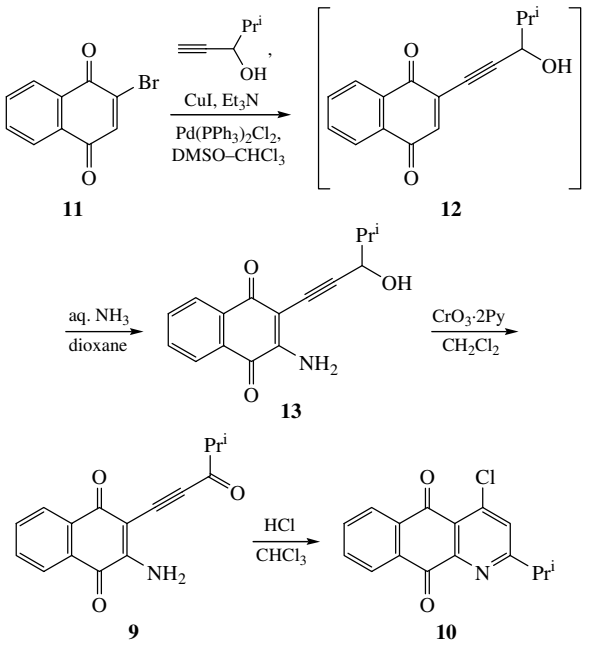
2b: mp 198–199 °C (toluene–hexane). ^{1}H NMR, δ: 1.45 (d, 6H, Me, *J* 6.9 Hz), 3.34 (sept., 1H, CH, *J* 6.9 Hz), 7.70–7.90 (m, 2H, $H^{8,9}$), 7.84 (s, 1H, H^3), 8.25–8.45 (m, 2H, $H^{7,10}$), 9.14 (s, 1H, H^5). Found (%): C, 58.20; H, 3.03; Br, 19.02; Cl, 8.44. Calc. for $C_{20}H_{13}BrClNO_2$ (%): C, 57.93; H, 3.16; Br, 19.27; Cl, 8.55.

3a: mp 252–253 °C (toluene–hexane). ^{1}H NMR, δ: 7.50–7.70 (m, 3H, Ph), 7.70–7.90 (m, 2H, $H^{9,10}$), 8.16 (s, 1H, H^3), 8.2–8.5 (m, 4H, $H^{8,11}$, Ph), 8.52 (d, 1H, $H^{5(6)}$, *J* 8.7 Hz), 8.63 (d, 1H, $H^{6(5)}$, *J* 8.7 Hz). Found (%): C, 74.95; H, 3.37; Cl, 9.77. Calc. for $C_{23}H_{12}ClNO_2$ (%): C, 74.70; H, 3.27; Cl, 9.59.

3b: mp 237–238 °C (toluene–hexane). ^{1}H NMR, δ: 7.50–7.70 (m, 3H, Ph), 7.70–7.90 (m, 2H, $H^{9,10}$), 8.38 (s, 1H, H^3), 8.20–8.45 (m, 2H, $H^{8,11}$), 8.51 (d, 1H, $H^{5(6)}$, *J* 8.7 Hz), 8.60 (d, 1H, $H^{6(5)}$, *J* 8.7 Hz). Found (%): C, 66.78; H, 2.98; Br, 19.40. Calc. for $C_{23}H_{12}BrNO_2$ (%): C, 66.69; H, 2.92; Br, 19.29.

4a: mp 194–195 °C (toluene–hexane). ^{1}H NMR, δ: 1.55 (s, 9H, Me), 7.75 (s, 1H, H^3), 7.70–7.90 (m, 2H, $H^{9,10}$), 8.20–8.40 (m, 2H, $H^{8,11}$), 8.48 (d, 1H, $H^{5(6)}$, *J* 8.6 Hz), 8.58 (d, 1H, $H^{6(5)}$, *J* 8.6 Hz). Found (%): C, 71.92; H, 4.56; Cl, 10.39. Calc. for $C_{21}H_{16}ClNO_2$ (%): C, 72.10; H, 4.61; Cl, 10.13.

4b: mp 188–189 °C (toluene–hexane). ^{1}H NMR, δ: 1.54 (s, 9H, Me), 7.70–7.90 (m, 2H, $H^{9,10}$), 7.95 (s, 1H, H^3), 8.20–8.40 (m, 2H, $H^{8,11}$), 8.47 (d, 1H, $H^{5(6)}$, *J* 8.8 Hz), 8.54 (d, 1H, $H^{6(5)}$, *J* 8.8 Hz). Found (%): C, 64.24; H, 4.28; Br, 20.00. Calc. for $C_{21}H_{16}BrNO_2$ (%): C, 63.97; H, 4.09; Br, 20.27.



Scheme 1

The generality of the method consists in its applicability to the synthesis of both haloquinolines and haloquinoline moieties in condensed polycyclic structures. Table 1 summarises the preparation of both a substituted quinoline and linear and angular fused tetracycles. The successful syntheses of polycyclic compounds **2**–**4** having a quinoid ring out of a quinoline fragment showed that electron-withdrawing substituents in the precursors do not influence the regioselectivity of the addition of hydrogen halides.

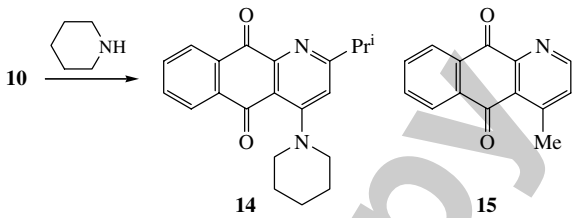
Note that, in the ^{1}H NMR spectra of compounds **2**–**4**, the disposition of the H^3 proton singlet depends on the nature of a halogen atom at the 4-position and a substituent at the 2-position. In the spectra of bromides **2b**, **3b** and **4b**, this singlet is shifted downfield relatively to the chemical shift of the H^3 proton in the spectra of chlorides **2a**, **3a** and **4a** ($\Delta\delta \approx 0.2$ ppm). The replacement of the alkyl group by an aryl (compounds **3a**,**b** and **4a**,**b**) provokes a considerable downfield shift of the H^3 singlet as well.

It was interesting to test the applicability of the method to the construction of a 4-haloquinoline-5,8-dione structural fragment as a new route to alkaloid cleistopholine derivatives and the antibiotic sampangin.[2(*b*),3] However, in this case, key acetylenic compounds should contain reactive amino and oxoalkynyl groups in a nonaromatic quinoid ring.

The direction and stereochemistry of hydrogen halides addition to such conjugated complex systems are not clearly understood. Nevertheless, we attempted to prepare 2-amino-3-(4-methyl-3-oxopentynyl)-1,4-naphthoquinone **9** and to use it as a key precursor for 4-chloro-2-isopropylbenzo[*g*]quinoline-5,10-dione **10** (Scheme 1).‡

A procedure for introducing several acetylenic substituents into the quinone ring was described.[12] We succeeded in applying it to the preparation of secondary acetylenic alcohol **12** from 2-bromo-1,4-naphthoquinone **11**. Because of its lability, alcohol **12** without isolation was aminated into the 3-position to give more stable aminoacetylenic alcohol **13**. Selective oxidation of **13** by an excess of the Collins reagent (8:1 by weight) at 0–2 °C afforded desired key ketone **9**. Ketone **9** reacts, like aminoarylynones **5**–**8**, with hydrogen chloride under conditions of the method giving heterocyclic quinone **10**. This example shows that the method can be applied to the synthesis of 4-haloquinoline-5,8-dione structures.

A halogen atom at the 4-position of a quinoline or quinolinedione moiety is labile and easily substituted by various functional hydrocarbon and heteroatomic groups. Some examples are presented here as an illustration.§



Scheme 2

Chlorazaanthraquinone **10** reacted readily with piperidine at 20 °C to give almost quantitatively 2-isopropyl-4-*N*-piperidinobenzo[*g*]quinoline-5,10-dione **14** (Scheme 2). Compound **14** is an amino analogue of alkaloid cleistopholine **15**.

The X-ray structure of **14** is shown in Figure 1.¶ In the molecule of this compound, benzene and pyridine rings are planar. In the quinone ring, the carbon C(4A) deviates from the plane of other atoms by 0.386 Å. Both substituents are turned relatively to the pyridine plane so that the torsion angles

‡ **13**: yield 47%, mp 143–144 °C (toluene). ^{1}H NMR, δ: 1.08, 1.11 (2d, 6H, Me_2C, *J* 6.7 Hz), 1.90–2.15 (m, 1H, CH), 2.94 (br. s, 1H, OH), 4.53 (d, 1H, HCO, *J* 5.6 Hz), 5.81 (br. s, 2H, NH_2), 7.55–7.80 (m, 2H, $H^{6,7}$), 7.95–8.15 (m, 2H, $H^{5,8}$). IR ($CHCl_3$, ν/cm^{-1}): 1645, 1677 (C=O), 2212 (C≡C), 3384, 3500 (NH_2), 3604 (OH). Found (%): C, 71.29; H, 5.77; N, 5.13. Calc. for $C_{16}H_{15}NO_3$ (%): C, 71.36; H, 5.61; N, 5.20.

9: yield 65%, mp 145–146 °C (toluene–hexane). ^{1}H NMR, δ: 1.31 (d, 6H, Me, *J* 6.9 Hz), 2.81 (sept., 1H, CH, *J* 6.9 Hz), 6.27, 6.46 (2br. s, 2H, NH_2), 7.60–7.85 (m, 2H, $H^{6,7}$), 8.00–8.20 (m, 2H, $H^{5,8}$). IR (ν/cm^{-1}): 1649, 1662, 1682 (C=O), 2181 (C≡C), 3375, 3492 (NH_2). Found (%): C, 71.70; H, 4.75; N, 5.19. Calc. for $C_{16}H_{13}NO_3$ (%): C, 71.90; H, 4.90; N, 5.24.

10: yield 68%, mp 122–123 °C (Et_2O–hexane). ^{1}H NMR, δ: 1.38 (d, 6H, Me, *J* 6.9 Hz), 3.34 (sept., 1H, CH, *J* 6.9 Hz), 7.60 (s, 1H, H^3), 7.70–7.90 (m, 2H, $H^{7,8}$), 8.20–8.40 (m, 2H, $H^{6,9}$). Found (%): C, 67.40; H, 3.99; Cl, 12.40. Calc. for $C_{16}H_{12}ClNO_2$ (%): C, 67.26; H, 4.23; Cl, 12.41.

§ **14**: yield 95%, mp 123–124 °C (Et_2O–hexane). ^{1}H NMR, δ: 1.34 (d, 6H, Me, *J* 6.9 Hz), 1.60–1.90 [m, 6H, $(CH_2)_3$], 3.21 (sept., 1H, CH, *J* 6.9 Hz), 3.25–3.40 (m, 4H, CH_2–N–CH_2), 6.93 (s, 1H, H^3), 7.65–7.85 (m, 2H, $H^{7,8}$), 8.15–8.30 (m, 2H, $H^{6,9}$). Found (%): C, 71.29; H, 6.21; N, 8.25. Calc. for $C_{20}H_{20}N_2O_3$ (%): C, 71.41; H, 5.99; N, 8.33.

16: yield 81%. ^{1}H NMR, δ: 0.98 (d, 6H, Me, *J* 6.8 Hz), 2.85 (sept., 1H, CH, *J* 6.8 Hz), 6.52 (s, 1H, H^3), 6.85–7.05 (m, 3H, OPh), 7.15–7.40 (m, 5H, OPh), 7.45–7.60 (m, 2H, OPh), 7.70–7.85 (m, 2H, $H^{8,9}$), 8.25–8.40 (m, 2H, $H^{7,10}$), 9.27 (s, 1H, H^5). UV [hexane, λ_{max}/nm (ε)]: 291 (30020), 486 (5770).

17: yield 80%, mp 244 °C (decomp., CH_2Cl_2). ^{1}H NMR, δ: 1.53 (s, 6H, Me), 2.16 (s, 1H, OH), 7.50–7.70 (m, 3H, Ph), 7.70–7.90 (m, 2H, $H^{9,10}$), 8.15 (s, 1H, H^3), 8.20–8.50 (m, 2H, $H^{8,11}$, Ph), 8.48 (d, 1H, $H^{5(6)}$, *J* 8.7 Hz), 8.59 (d, 1H, $H^{6(5)}$, *J* 8.7 Hz). IR (ν/cm^{-1}): 1660, 1673 (C=O), 2220 (C≡C), 3392 (OH). Found (%): C, 80.30; H, 4.42; N, 3.51. Calc. for $C_{28}H_{19}NO_3$ (%): C, 80.56; H, 4.59; N, 3.35.

¶ The X-ray analysis of compound **14** was performed on a Bruker P4 diffractometer using MoKα radiation with a graphite monochromator. The crystals are orthorhombic: a = 15.998(1), b = 12.864(1) and c = = 17.093(2) Å, V = 3517.8(6) Å^3, space group *Pbca*, Z = 8, $C_{21}H_{22}N_2O_2$, M = 334.41, $F(000)$ = 1424, μ = 0.082 cm^{-1}, d_{calc} = 1.263 g cm^{-3}, T = 293 K, crystal size, 0.48×0.38×0.24 mm. The intensities of 3453 independent reflections with $2\theta < 52°$ were measured using the $\theta/2\theta$ scanning technique. The structure was solved by a direct method using the SHELX-97 programs (S-97 and L-97) and refined by the least squares method in a full-matrix anisotropic–isotropic (for hydrogen atoms) approximation to $wR_2 = 0.1699$, $S = 1.005$ for all reflections [$R_1 = 0.0567$ for 2037 reflections with $I \geq 2\sigma(I)$]. The positions of hydrogen atoms were obtained from calculated geometrical and refined in riding model.

CCDC 645254 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2008.

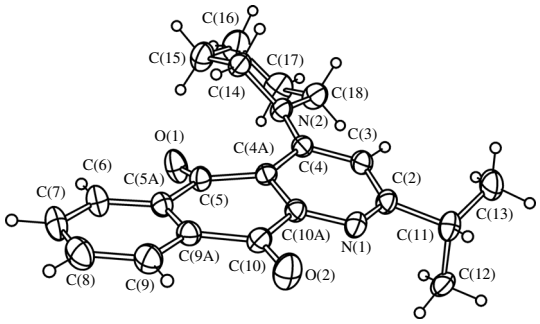
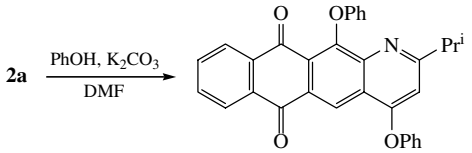


Figure 1 X-ray structure of **14**.

C(3)–C(4)–N(2)–C(18) and C(3)–C(2)–C(11)–C(13) are 11.74° and 31.14°, respectively.



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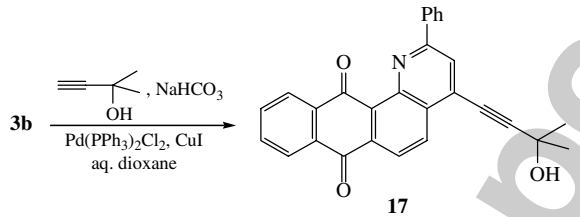
Scheme 3

In compound **2a**, both chlorine atoms are replaced by phenoxy groups under the action of phenol in the presence of K_2CO_3 in DMF at 120 °C (Scheme 3). 2-Isopropyl-4,12-diphenoxynaphtho-[2,3-*g*]quinoline-6,11-dione **16** is a heterocyclic analogue of the known photochrome phenoxynaphthacenequinone.[13]

The cross-coupling of bromide **3b** with 2-methylbut-3-yn-2-ol demonstrates the possibility of introducing reactive acetylenic groups into prepared heterocyclic compounds (Scheme 4).



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Scheme 4

Thus, *vic*-3-oxoalk-1-ynyl substituted aromatic amines react with hydrogen halides under mild conditions to close the halopyridine ring. This tandem hydrohalogenation–cyclization process is a general method for the formation of 4-haloquinoline and 4-haloquinoline-5,8-dione moieties in polycyclic compounds.

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