A REGIOSELECTIVE SYNTHESIS OF 2-ALKYLFURO[3,2-c]QUINOLIN-4(5H)-ONES

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Abstract - The title compounds (**2a-h**) were obtained in moderate yields by simply refluxing 1-alkyl-4-hydroxyquinolin-2(1H)-ones (**1a,b**) with a number of acetylenic halides in n-butanol in the presence of anhydrous potassium carbonate. Compounds (**2h,i**) were also obtained from 4-[2'-chloroprop-2-enyloxy][1]quinolin-2(1H)-ones (**11a,b**) via [3,3] sigmatropic rearrangement and cyclisation of the intermediate chloroallylic enols (**13a,b**) with aqueous ethanolic potassium hydroxide.

Various substituted furo[3,2-c]quinolin-4(5H)-ones are abundant in the plant kingdom[1]. Available routes to the synthesis of substituted furo[3,2-c]quinolin-4(5H)-ones include condensation of diethyl 2-propargyl malonate with aromatic amines[2], 3-halo-4-hydroxy-1-alkylquinolin-2(1H)-one with copper isopropenylacetylide[3], Claisen rearrangement of 4-allyloxyquinoline followed by cyclisation[4], cyclodehydraion of β-keto ethers of quinolin-2(1H)-ones[5] and phase-transfer catalysed alkylation of 4-hydroxyquinolin-2(1H)-one with propargyl bromide to give a mixture of six different products[6]. Based on our recent observation[7] on the one-step synthesis of thieno[2,3-b]thiochromones we have developed a direct route to 5-alkyl-2-alkylfuro[3,2-c]quinolin-4(5H)-ones. Here we report the results of our investigation.

When a mixture of 1-alkyl-4-hydroxyquinolin-2(1H)-ones (**1a** or **1b**), acetylenic halide viz. 2-bromo-3-butyne, 4-chloro-1-phenoxybut-2-yne, 1-(4'-bromophenoxy)-4-chlorobut-2-yne, 4-chloro-1-(4'-chlorophenoxy)but-2-yne, 1-(2'-chlorophenoxy)-4-chlorobut-2-yne or, propargyl bromide, was refluxed in 1-butanol in the presence of potassium carbonate for 10 h gave substituted furo-[3,2-c]quinolin-4(5H)-ones (**2a-h**) in 22-60% yield. Additionally unreacted starting materials (**1a** or **1b**, 19-42%) were also recovered from the reaction mixture along with untractable liquid mixture. The O-H absorption band at 3460 cm^{-1} in starting materials (**1a** and **b**) is absent in the products (**2a-h**). The products (**2a-h**) exhibit uv absorption maxima in the vicinity of 240, 292, 325 and 340 nm; ir absorption band among others at 1650 cm^{-1} (-N-C(=O)-); nmr shows the formation of a new methyl group at δ 2.40-2.68.

The 1-alkyl-4-hydroxyquinolin-2(1H)-one in the presence of a base can form an ambident anion with several nucleophilic sites (**3**, **4** and **5**). The formation of furo[3,2-c]quinolin-4(5H)-ones (**2a** and **b**) from 1 is explicable via the SN_2-displacement of the bromine of 3-bromo-1-butyne by the anion (**4**)

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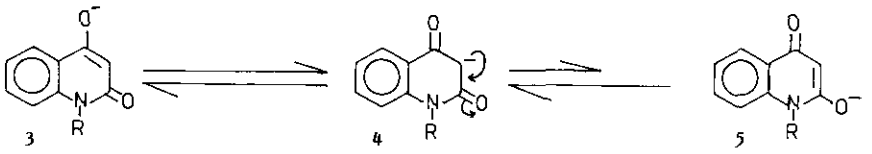
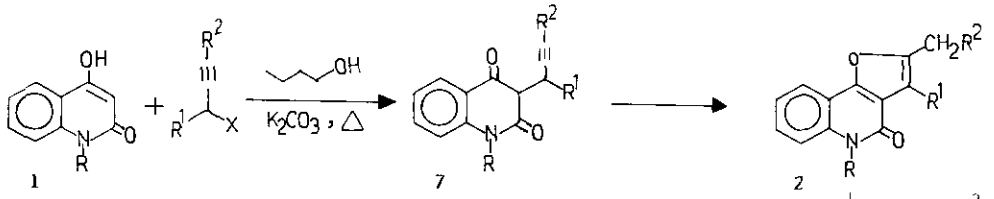


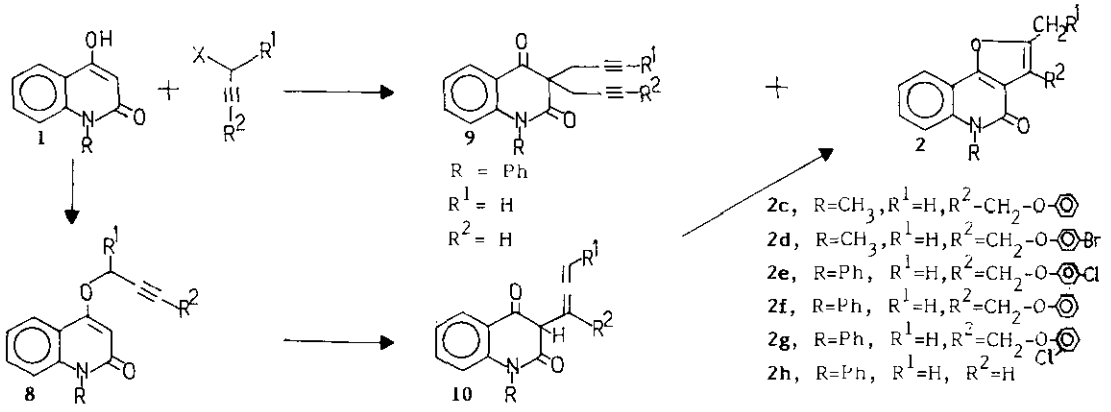
to give **7** (C-alkylation) followed by nucleophilic ring closure to give products (**2a**) and (**2b**) (Scheme 1). 2-Bromo-2-methyl-3-butyne does not react at all perhaps due to steric interaction between the anion (**4**) and the bromine containing tetrasubstituted C-atom. However, the chlorine of 1-aryloxy-4-chlorobut-2-yne was replaced by anion (**3**) to give ethers (**8**) which under the reaction



2a, R=CH_3, R^1 = CH_3, R^2=H

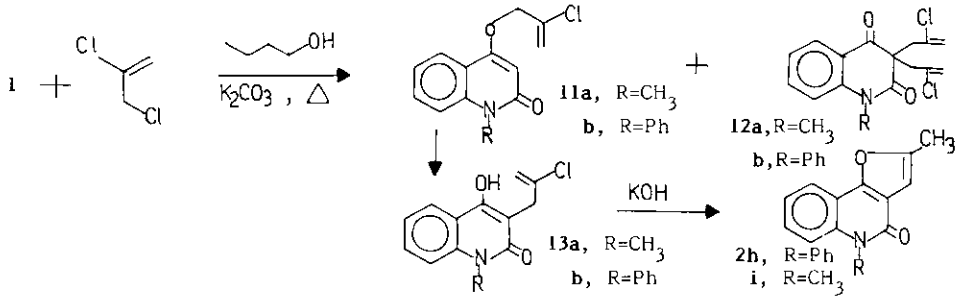
Scheme 1 **2b**, R=Ph, R^1 = CH_3, R^2=H

conditions suffered a [3,3]sigmatropic rearrangement to give allenylenol which under base catalysis[8,9] gave the furo[3,2-c]quinolin-4(5H)-one (**2c-h**) (Scheme 2).



Scheme 2

We next considered a different route for the synthesis of furo[3,2-c]quinolin-4(5H)-ones (**2h** and **i**) from 2,3-dichloropropene. 4-Hydroxy-1-alkylquinolin-2(1H)-ones (**1a** and **b**) reacted with 2,3-dichloropropene to give ethers (**11a** and **b**) (42-55%) along with C,C-dialkylated product (**12a** and **b**) (15-23%). The ethers (**11a** and **b**) smoothly rearranged to chloroallylic enols (**13a** and **b**) in quantitative yield when refluxed in chlorobenzene or in N,N-dimethylaniline. Our attempt to cyclise these enols (**13a** and **b**) by refluxing in N,N-diethylaniline[10] or by treating with cold conc. H_2SO_4[11] failed. However, these were successfully cyclised to 2-methylfuro[3,2-c]quinolin-4(5H)-ones by refluxing in 5-8% aqueous ethanolic potassium hydroxide for 16 h (Scheme 3).



Scheme 3

In summary it can be concluded that the second method for the synthesis of the title compounds is a regioselective one whereas the first method is a simple one-step process.

EXPERIMENTAL

The melting points were recorded on sulphuric acid and are uncorrected. Uv absorption spectra were recorded on a Hitachi 200-20 spectrophotometer. Ir spectra were run for KBr discs on a Perkin-Elmer-1330 infrared spectrophotometer. ^{1}H-Nmr spectra were determined for solutions in deuteriochloroform with $SiMe_4$ as internal standard on JEOL FX-100 (100 MHz) spectrometer at the Indian Institute of Chemical Biology (Calcutta).

Preparation of compound (**2a-h**), **9**, (**11a** and **b**) and (**12a** and **b**) :

A mixture of 1-alkyl-4-hydroxyquinolin-2(1H)-ones (6 mmol; **1a**, R=CH_3; **1b**, R=Ph) and 7 mmol of each of the following acetylenic halides, 2-bromo-but-3-yne, 4-chloro-1-phenoxybut-2-yne, 1-[4'-bromophenoxy]-4-chlorobut-2-yne, 1-[4'-chlorophenoxy]-4-chlorobut-2-yne, 1-[2'-chlorophenoxy]-4-chlorobut-2-yne or, propargyl bromide was refluxed in dry n-butanol (50 ml) in the presence of anhydrous potassium carbonate (2 g) for 10 h. The reaction mixture was cooled, filtered, and the solvent was removed. The residual mass was extracted with chloroform (3 x 50 ml). The extract was washed with brine (2 x 50 ml), water (25 ml) and dried (Na_2SO_4). After removal of the solvent, the crude mass was chromatographed on silica gel (Qualigen, 60-120 mesh). The products were obtained when the column was eluted with benzene : pet. ether (bp 60-80 °C) 1:1 (**2a**), chloroform (**2b**), benzene (**2c**), benzene : pet. ether (bp 60-80 °C) 1:3 (**2d**), benzene (**2e**) chloroform (**2f, h**), benzene (**2g**), benzene (**9**), benzene (**11a**), chloroform (**11b**), pet. ether (bp 60-80 °C), (**12a**), benzene : pet. ether (bp 60-80 °C) 1:1 (**12b**).

Compound (**2a**) : Yield 44% [also 20% of starting material (**1a**) recovered], mp 146 °C,uv ($CHCl_3$): λ_{max} 240, 295, 330, 345 nm; ir : ν_{max} 2960, 1650 (C=O), 1320 (C-O-C, cyclic); nmr : δ 2.36 (s, 3H, 3-CH_3), 2.40 (s, 3H, 2-CH_3), 3.96 (s, 3H, 5-CH_3), 7.28-7.52 (m, 3H, ArH), 7.92-8.00 (m, 1H, ArH); ms : m/z 227(M^+), 226, 212, 198, 184; Anal. calcd for $C_{14}H_{13}NO_2$: C, 74.00; H, 5.72; N, 6.16. Found : C, 73.79;H, 5.48; N, 6.17.

Compound (**2b**) Yield 60% [also 31% of starting material (**1b**) recovered], mp 238 °C,uv ($CHCl_3$) :

λ_{max} 240, 293, 325, 342 nm; ir : ν_{max} 2930, 1680, (C=O), 1325 (C-O-C, cyclic); nmr : δ 2.34 (s, 3H, 3-CH_3), 2.44 (s, 3H, 2-CH_3), 7.20-7.68 (m, 8H, ArH), 7.88-8.08 (m, 1H, ArH); Anal. cald for $C_{19}H_{15}NO_2$: C, 78.89; H, 5.19; N, 4.84. Found : C, 79.09; H, 5.45; N, 4.82.

Compound (**2c**) Yield 41% [also 38% of starting material (**1a**) recovered], mp 184 °C, uv ($CHCl_3$) : λ_{max} 240, 295, 325, 340 nm; ir : ν_{max} 1650 (C=O), 1320 (C-O-C, cyclic); nmr : δ 2.54 (s, 3H, 2-CH_3), 3.76 (s, 3H, 5-CH_3), 5.44 (s, 2H, OCH_2), 7.20-7.60 (m, 7H, ArH), 7.92-8.04 (m, 1H, ArH); Anal. Cald for $C_{20}H_{17}NO_3$: C, 75.23; H, 5.32; N, 4.38. Found : C, 75.10; H, 5.02; N, 4.39.

Compound (**2d**) Yield 22% [also 30% of starting material (**1a**) recovered], mp 172 °C; uv ($CHCl_3$) : λ_{max} 240, 292, 325, 340 nm; ir : ν_{max} 2920, 1650 (C=O), 1320 (C-O-C, cyclic); nmr : δ 2.50 (s, 3H, 2-CH_3), 3.70 (s, 3H, 5-CH_3), 5.40 (s, 2H, -OCH_2), 7.20-7.60 (m, 7H,ArH), 7.88-8.00 (m, 1H, ArH); Anal. Calcd for $C_{20}H_{16}NO_3Br$: C, 60.30; H, 4.02; N, 3.51. Found : C, 60.05; H, 3.89; N, 3.55.

Compound (**2e**) Yield 35% [also 42% of starting material (**1b**) recovered], mp 188-189 °C, uv ($CHCl_3$): λ_{max} 240, 292, 325, 340 nm; ir : ν_{max} 2980, 1670 (C=O), 1310 (C-O-C, cyclic), 1240 (C-O-C, open); nmr : δ 2.60 (s, 3H, 2-CH_3), 5.40 (s, 2H, -OCH_2), 7.16-7.76 (m, 12H, ArH), 7.96-8.16 (m, 1H, ArH); Anal. Calcd for $C_{25}H_{18}NO_3Cl$: C, 72.28; H, 4.33; N, 3.37. Found : C, 72.53; H, 4.40; N, 3.35.

Compound (**2f**) Yield 40% [also 28% of starting material (**1b**) recovered], mp 150 °C, uv ($CHCl_3$) : λ_{max} 240, 295, 325, 340 nm; ir : ν_{max} 2940, 1680 (C=O), 1310 (C-O-C, cyclic); nmr : δ 2.60 (s, 3H, 2-CH_3), 5.44 (s, 2H, -OCH_2), 7.20-7.68 (m, 13H, ArH), 7.92-8.08 (m, 1H, ArH); Anal. Calcd for $C_{25}H_{19}NO_3$: C, 78.74; H, 4.98; N, 3.67. Found : C, 78.84; H, 5.28; N, 3.66.

Compound (**2g**) Yield 35% [also 28% of starting material (**1b**) recovered], mp 209 °C, uv ($CHCl_3$) : λ_{max} 242, 283, 295, 325, 340 nm; ir : ν_{max} 2940, 1680 (C=O), 1320 (C-O-C, cyclic); nmr : δ 2.68 (s, 3H, 2-CH_3), 5.56 (s, 2H, -OCH_2), 7.16-7.72 (m, 12H, ArH), 7.96-8.08 (m, 1H, ArH); Anal. Calcd for $C_{25}H_{18}NO_3Cl$: C, 72.28; H, 4.33; N, 3.37. Found : C, 72.40; H, 4.38; N, 3.36.

Compound (**2h**) Yield 44%, mp 190 °C; uv ($CHCl_3$) : λ_{max} 240, 292, 323, 340 nm; ir : ν_{max} 3100, 1680 (C=O), 1320 (C-O-C, cyclic); nmr : δ 2.48-2.68 (d, J = 1.5 Hz, 3H, 2-CH_3), 6.04-6.76 (m, 1H), 7.24-7.60 (m, 8H, ArH), 7.96-8.08 (m, 1H, ArH); Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.54; H, 4.72; N, 5.09. Found : C, 78.60; H, 4.75; N, 5.08.

Compound (**9**) Yield 38%, mp. 124 °C; uv ($CHCl_3$) : λ_{max} 242, 350 nm; ir : ν_{max} 3300, 2140, 1680 (C=O), 1700 (C=O); nmr : δ 1.92 (t, J = 3 Hz, 2H, CH_2-C≡CH), 2.92 (d, J=3Hz, 4H, CH_2-C≡CH) 7.20-7.64 (m, 8H, ArH), 8.08-8.20 (m, 1H, ArH); Anal. Calcd for $C_{21}H_{15}NO_2$: C, 80.51; H, 4.79; N, 4.47. Found : C, 80.74; H, 4.90; N, 4.46.

Compound (**11a**) Yield 42%, mp 140 °C; uv ($CHCl_3$) : λ_{max} 240, 270, 280, 320 nm; ir : ν_{max} 3100, 1650 (C=O), 1255 (C-O-C); nmr : δ 3.64 (s, 3H, N-C**H**$_3$), 4.68 (s, 2H, -OC**H**$_2$), 5.52-5.60 (m, 2H, =C**H**$_2$), 6.00 (s, 1H, C=C**H**), 7.20-7.40 (m, 3H, Ar**H**), 7.96-8.08 (m, 1H, Ar**H**); Anal. Calcd for $C_{13}H_{12}NO_2Cl$: C, 62.65; H, 4.81; N, 5.62. Found : C, 62.50; H, 4.75; N, 5.65.

Compound (**11b**) Yield 55%, mp 167 °C; uv ($CHCl_3$) : λ_{max} 240, 270, 280, 320 nm; ir : ν_{max} 3100, 1650 (C=O), 1256 (C-O-C); nmr : δ 4.76 (s, 2H, -OC**H**$_2$), 5.60-5.68 (m, 2H, CH_2-$\overset{Cl}{\overset{|}{C}}$=C**H**$_2$), 6.10 (s, 1H, C=C**H**), 7.20-7.64 (m, 8H, Ar**H**), 8.00-8.12 (m, 1H, Ar**H**); Anal. Calcd for $C_{18}H_{14}NO_2Cl$: C, 69.45; H, 4.50; N, 4.50. Found : C, 69.55; H, 4.59; N, 4.495.

Compound (**12a**) Yield 23%, mp 95 °C; uv ($CHCl_3$) : λ_{max} 240, 345 nm; ir : ν_{max} 2940, 1650 (C=O), 1690 (C=O); nmr : δ 3.08 (s, 4H, -C-C**H**$_2$), 3.44 (s, 3H, N-C**H**$_3$), 5.04-5.08 (t, J=2Hz, 4H, =C**H**$_2$), 7.08-7.72 (m, 3H, Ar**H**), 8.00-8.12 (m, 1H, Ar**H**); Anal. Calcd for $C_{16}H_{15}NO_2Cl_2$: C, 59.44; H, 4.64; N, 4.33. Found : C, 59.35; H, 4.38; N, 4.41.

Compound (**12b**) Yield 15%, mp 120 °C; uv ($CHCl_3$) : λ_{max} 240, 345 nm; ir : ν_{max} 2960, 1670 (C=O), 1700 (C=O); nmr : δ 3.18 (s, 4H, -C-C**H**$_2$), 5.24 (t, J=2Hz, 4H, =C**H**$_2$), 7.08-7.72 (m, 8H, Ar**H**), 8.04-8.20 (m, 1H, Ar**H**); Anal. Calcd for $C_{21}H_{17}NO_2Cl_2$: C, 65.45; H, 4.41; N, 3.63. Found : C, 65.50; H, 4.62; N, 3.59.

Rearrangement of compound **11a** and **11b** :

1-Alkyl-4-[2'-chloro-2-propenyloxy]quinolin-2-one (0.5 g, 2.0 mmol, **11a** or **b**) was refluxed in chlorobenzene (2 ml) for 10 h. Chlorobenzene was removed under reduced pressure and the residual mass was chromatographed over silica gel (Qualigen 60-120 mesh). Elution of the column with benzene gave a solid (**13a** or **13b**).

Compound (**13a**) Yield 92.4% (0.46 g), mp 184-186 °C; uv ($CHCl_3$) : λ_{max} 240, 275, 285, 325 nm; ir : ν_{max} 3200 (O-H), 1650 (C=O), 1600 (C=C); nmr : δ 3.72 (s, 3H, N-C**H**$_3$), 3.84 (s, 2H, C-C**H**$_2$), 5.32-5.40 (m, 2H, =C**H**$_2$), 7.28 (s, 1H, O-**H**), 7.32-7.68 (m, 3H, Ar**H**), 8.00-8.12 (m, 1H, Ar**H**); Anal. Calcd for $C_{13}H_{12}NO_2Cl$: C, 62.65; H, 4.81; N, 5.62. Found : C, 62.62; H, 4.80; N, 5.64.

Compound (**13b**) Yield 72.2% (0.45 g), mp 233 °C; uv ($CHCl_3$) : λ_{max} 240, 275, 285, 325 nm; ir : ν_{max} 3160, 1640 (C=O); nmr : δ 3.82 (s, 2H, -C-C**H**$_2$), 5.22 (m, 2H, =C**H**$_2$), 7.26 (s, 1H, O-**H**), 7.30-7.72 (m, 8H, Ar**H**), 8.08-8.24 (m, 1H, Ar**H**); Anal. Calcd for $C_{18}H_{14}NO_2Cl$: C, 69.45; H, 4.50; N, 4.50. Found : C, 69.49; H, 4.55; N, 4.49.

Attempted cyclisation of compound **11a** and **b** in diethylaniline (DEA) :

Compound **11a** or **11b** (0.2 g) was refluxed in N,N-diethylaniline (2 ml) for 8 h. Diethylaniline was then removed in vacuo, the residual mass was taken in chloroform (50 ml) and washed with 6N HCl (3 x 25 ml), water (3 x 25 ml) and dried (Na_2SO_4). After removal of the solvent, the crude mass was chromatographed on silica gel (Qualigen, 60-120 mesh), a white solid was obtained when the

column is eluted with chloroform. Compound (**11a**) gave compound (**13a**), yield (90%), mp 184-186 °C. This was shown to be identical with the rearranged compound (**13a**), by tlc, mixed mp and superimposable ir. Compound (**11b**) gave compound (**13b**) yield (85%), mp 233 °C. This was again shown to be identical with the rearranged product (**13b**) by tlc, mixed mp and superimposable ir.

Cyclisation of **13a** and **13b** :

Compound **13a** or **13b** (0.1 g) was refluxed in 2 ml of ethanolic potassium hydroxide solution (5% for **13a** and 8% for **13b**) for 16 h. Ethanol was then removed, the residual mass was taken in chloroform (25 ml) and washed with water (10 x 25 ml) and dried (Na_2SO_4). After removal of the solvent, the crude mass was recrystallized from chloroform-hexane.

Compound (**2h**)[12] Yield 70% (0.07 g), mp 190 °C; uv ($CHCl_3$) : λ_{max} 240, 292, 325, 340 nm; ir : ν_{max} 2960, 1670, 1310 (C-O-C); nmr : δ 2.48-2.68 (d, J=1.5 Hz, 3H, CH_3), 6.04-6.76(m, 1H), 7.24-7.60 (m, 8H, ArH), 7.96-8.08 (m, 1H, ArH).

Compound (**2i**)[12] Yield 80% (0.08 g), mp 118 °C; uv ($CHCl_3$) : λ_{max} 240, 292, 325, 340 nm; ir : ν_{max} 2940, 1670 (C=O), 1320 (C-O-C); nmr : δ 2.44-2.52 (d, J=1.5 Hz, 3H, CH_3), 3.76 (s, 3H, N-CH_3), 3.76 (s,3H, N-CH_3), 6.00-6.70 (m, 1H), 7.28-7.68 (m, 3H, ArH), 8.00-8.12 (m, 1H, ArH).

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