

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

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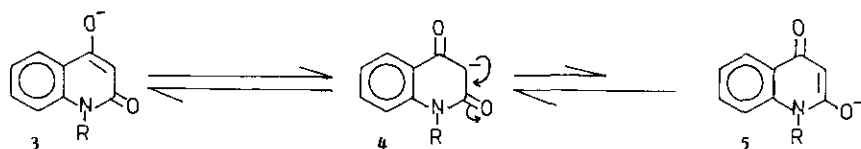
Abstract - The title compounds (**2a-h**) were obtained in moderate yields by simply refluxing 1-alkyl-4-hydroxyquinolin-2(1H)-ones (**1a,b**) with a number of acetylenic halides in *n*-butanol in the presence of anhydrous potassium carbonate. Compounds (**2h,i**) were also obtained from 4-[2'-chloroprop-2-enyloxy][1]quinolin-2(1H)-ones (**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 kingdom¹. Available routes to the synthesis of substituted furo[3,2-c]quinolin-4(5H)-ones include condensation of diethyl 2-propargyl malonate with aromatic amines², 3-halo-4-hydroxy-1-alkylquinolin-2(1H)-one with copper isopropenylacetylde³, Claisen rearrangement of 4-allyloxyquinoline followed by cyclisation⁴, cyclodehydration of β -keto ethers of quinolin-2(1H)-ones⁵ and phase-transfer catalysed alkylation of 4-hydroxyquinolin-2(1H)-one with propargyl bromide to give a mixture of six different products⁶. Based on our recent observation⁷ 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.

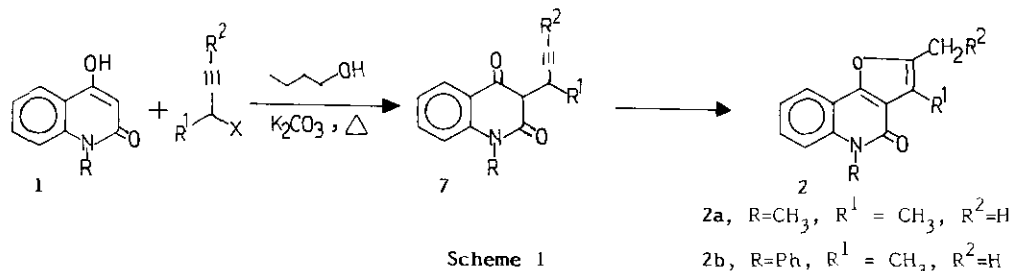
When a mixture of 1-alkyl-4-hydroxyquinolin-2(1H)-ones (**1a** or **1b**), acetylenic halide viz. 2-bromo-3-butyne, 4-chloro-1-phenoxybut-2-yne, 1-(4'-bromophenoxy)-4-chlorobut-2-yne, 4-chloro-1-(4'-chlorophenoxy)but-2-yne, 1-(2'-chlorophenoxy)-4-chlorobut-2-yne or, propargyl bromide, was refluxed in 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-); 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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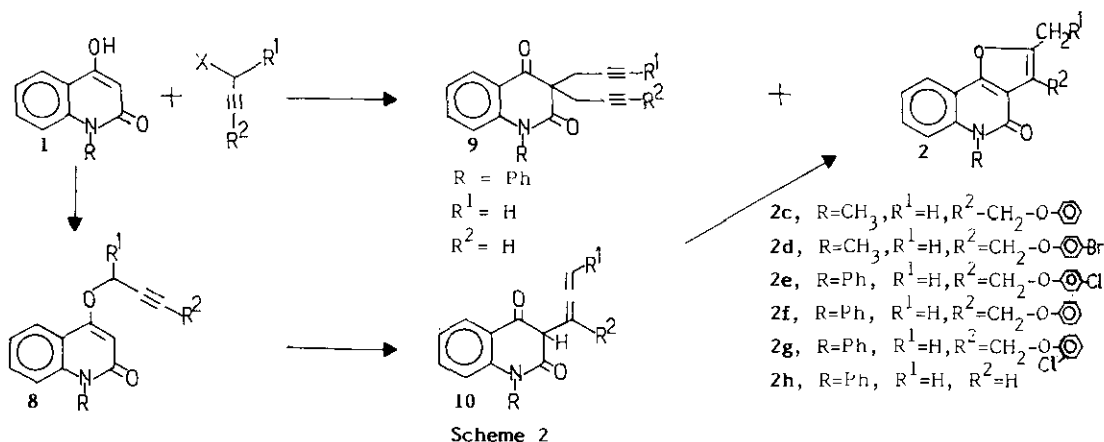


to give 7 (C-alkylation) followed by nucleophilic ring closure to give products (2a) and (2b) (Scheme 1). 2-Bromo-2-methyl-3-butyne does not react at all perhaps due to steric interaction between the anion (4) and the bromine containing tetrasubstituted C-atom. However, the chlorine of 1-aryloxy-4-chlorobut-2-yne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



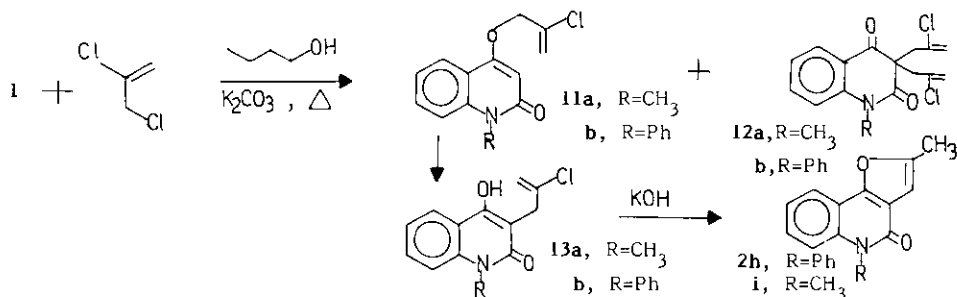
Scheme 1

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-diethylaniline¹⁰ or by treating with cold conc. H₂SO₄¹¹ 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. ¹H-Nmr spectra were determined for solutions in deuteriochloroform with SiMe₄ 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=CH₃; 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 (Na₂SO₄). 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 (CHCl₃): 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-CH₃), 2.40 (s, 3H, 2-CH₃), 3.96 (s, 3H, 5-CH₃), 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 C₁₄H₁₃NO₂ : 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 (CHCl₃) :

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-CH₃), 2.44 (s, 3H, 2-CH₃), 7.20-7.68 (m, 8H, ArH), 7.88-8.08 (m, 1H, ArH); Anal. calcd for C₁₉H₁₅NO₂ : 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 (CHCl₃) : 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-CH₃), 3.76 (s, 3H, 5-CH₃), 5.44 (s, 2H, OCH₂), 7.20-7.60 (m, 7H, ArH), 7.92-8.04 (m, 1H, ArH); Anal. Calcd for C₂₀H₁₇NO₃ : 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 (CHCl₃) : 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-CH₃), 3.70 (s, 3H, 5-CH₃), 5.40 (s, 2H, -OCH₂), 7.20-7.60 (m, 7H, ArH), 7.88-8.00 (m, 1H, ArH); Anal. Calcd for C₂₀H₁₆NO₃Br : 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 (CHCl₃): 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-CH₃), 5.40 (s, 2H, -OCH₂), 7.16-7.76 (m, 12H, ArH), 7.96-8.16 (m, 1H, ArH); Anal. Calcd for C₂₅H₁₈NO₃Cl : 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 (CHCl₃) : 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-CH₃), 5.44 (s, 2H, -OCH₂), 7.20-7.68 (m, 13H, ArH), 7.92-8.08 (m, 1H, ArH); Anal. Calcd for C₂₅H₁₉NO₃ : 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 (CHCl₃) : 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-CH₃), 5.56 (s, 2H, -OCH₂), 7.16-7.72 (m, 12H, ArH), 7.96-8.08 (m, 1H, ArH); Anal. Calcd for C₂₅H₁₈NO₃Cl : 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 (CHCl₃) : 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-CH₃), 6.04-6.76 (m, 1H), 7.24-7.60 (m, 8H, ArH), 7.96-8.08 (m, 1H, ArH); Anal. Calcd for C₁₈H₁₃NO₂ : 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 (CHCl₃) : 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, CH₂-C≡CH), 2.92 (d, J=3Hz, 4H, CH₂-C≡CH) 7.20-7.64 (m, 8H, ArH), 8.08-8.20 (m, 1H, ArH); Anal. Calcd for C₂₁H₁₅NO₂ : 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 (CHCl₃) : 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-CH₃), 4.68 (s, 2H, -OCH₂), 5.52-5.60 (m, 2H, =CH₂), 6.00 (s, 1H, C=CH), 7.20-7.40 (m, 3H, ArH), 7.96-8.08 (m, 1H, ArH); Anal. Calcd for C₁₃H₁₂NO₂Cl : 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 (CHCl₃) : λ_{\max} 240, 270, 280, 320 nm; ir : ν_{\max} 3100, 1650 (C=O), 1256 (C-O-C); nmr : δ 4.76 (s, 2H, -OCH₂), 5.60-5.68 (m, 2H, CH₂-C=CH₂), 6.10 (s, 1H, C=CH), 7.20-7.64 (m, 8H, ArH), 8.00-8.12 (m, 1H, ArH); Anal. Calcd for C₁₈H₁₄NO₂Cl : 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 (CHCl₃) : λ_{\max} 240, 345 nm; ir : ν_{\max} 2940, 1650 (C=O), 1690 (C=O); nmr : δ 3.08 (s, 4H, -C-CH₂), 3.44 (s, 3H, N-CH₃), 5.04-5.08 (t, J=2Hz, 4H, =CH₂), 7.08-7.72 (m, 3H, ArH), 8.00-8.12 (m, 1H, ArH); Anal. Calcd for C₁₆H₁₅NO₂Cl₂ : 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 (CHCl₃) : λ_{\max} 240, 345 nm; ir : ν_{\max} 2960, 1670 (C=O), 1700 (C=O); nmr : δ 3.18 (s, 4H, -C-CH₂), 5.24 (t, J=2Hz, 4H, =CH₂), 7.08-7.72 (m, 8H, ArH), 8.04-8.20 (m, 1H, ArH); Anal. Calcd for C₂₁H₁₇NO₂Cl₂ : 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 (CHCl₃) : 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-CH₃), 3.84 (s, 2H, C-CH₂), 5.32-5.40 (m, 2H, =CH₂), 7.28 (s, 1H, O-H), 7.32-7.68 (m, 3H, ArH), 8.00-8.12 (m, 1H, ArH); Anal. Calcd for C₁₃H₁₂NO₂Cl : 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 (CHCl₃) : λ_{\max} 240, 275, 285, 325 nm; ir : ν_{\max} 3160, 1640 (C=O); nmr : δ 3.82 (s, 2H, -C-CH₂), 5.22 (m, 2H, =CH₂), 7.26 (s, 1H, O-H), 7.30-7.72 (m, 8H, ArH), 8.08-8.24 (m, 1H, ArH); Anal. Calcd for C₁₈H₁₄NO₂Cl : 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 (Na₂SO₄). 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 tic, 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 tic, 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 (Na₂SO₄). 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 (CHCl₃) : 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, CH₃), 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 (CHCl₃) : 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, CH₃), 3.76 (s, 3H, N-CH₃), 3.76 (s, 3H, N-CH₃), 6.00-6.70 (m, 1H), 7.28-7.68 (m, 3H, ArH), 8.00-8.12 (m, 1H, ArH).

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