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Regioselective Synthesis of Pyrano[3,2-*f*]quinolin-2(7*H*)-ones and Furo[3,2-*f*]quinolin-2-ones

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Summary. A simple and efficient synthesis of the hitherto unreported ring systems pyrano[3,2-*f*]quinolin-2(7*H*)-one and furo[3,2-*f*]quinolin-2-one was accomplished *via* a thermal [3,3]-sigmatropic rearrangement.

Keywords. Cyclizations; 5,6-Fused quinolones; Heterocycles; Sigmatropic rearrangement.

Introduction

Quinolone alkaloids are known to possess antimicrobial activity and marked cytotoxicity against animal and plant tumors [1]. A novel class of 4-hydroxyquinolin-2(1*H*)-ones has recently been described [2] as selective glycinesite *NMDA* antagonists with potent *in vivo* activity after oral administration. However, depending on their structural types, quinolone derivatives exhibit different activities [3]. Furo[2,3-*c*]quinolin-4(5*H*)-one and 2*H*-pyrano[3,2-*c*]quinolin-5(6*H*)-one derivatives are abundantly distributed in nature [4]. A number of syntheses for these heterocycles including those from our own work have been reported [5, 6]. Continued interest in this area prompted us to undertake the present investigation on the thermal rearrangement of different 6-allyloxy- and prop-2-ynyloxyquinolin-2(1*H*)-ones.

Results and Discussion

The starting materials **3a–e** were synthesized in 70–75% yield by treating 6-hydroxy-1-methylquinolin-2(1*H*)-one (**1**) with different propynylic and allylic halides (**2**) in refluxing acetone in the presence of anhydrous potassium carbonate for 10 h (Scheme 1).

A thermal [3,3]-sigmatropic rearrangement was utilized for the synthesis of the pyrano- and furano-quinolones. The pyrano[3,2-*f*]quinolin-2(7*H*)-ones **4a**,**b** were obtained in 60–65% yield by heating the propargyl ethers **3a**,**b** in refluxing N,N-

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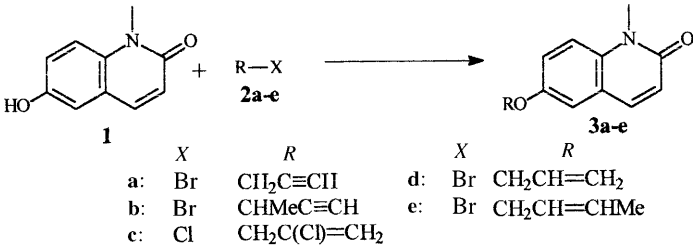
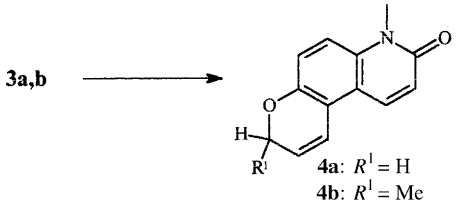


Scheme 1

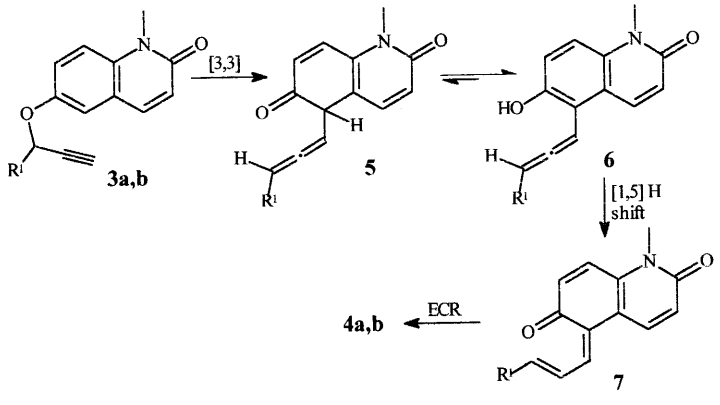


Scheme 2

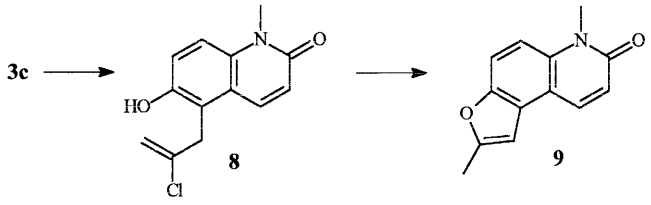
diethylaniline for 12 h (Scheme 2). There was no indication for the formation of furanoquinolone even in the crude reaction mixture.

The formation of the pyrano[3,2-*f*]quinolin-2(7*H*)-ones **4a**,**b** may be rationalized by the initial [3,3]-sigmatropic rearrangement of the propargyl ethers **3a**,**b** to the allenyl derivatives **5** followed by enolization, [1,5]-hydrogen shift, and electrocyclic ring closure [7] to give the products **4a**,**b** (Scheme 3).

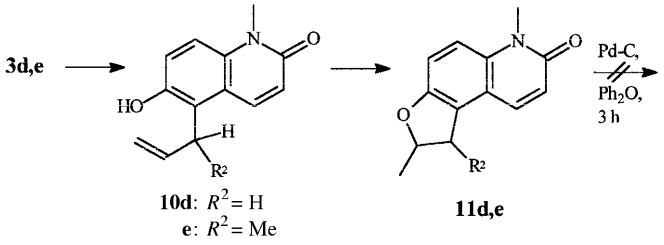
The furo[3,2-*f*]quinolin-2-one derivatives **9** and **11** were synthesized *via* two different routes. In one route, the chloropropenyl ether **3c** was heated in refluxing N,N-diethylaniline for 12 h to give the corresponding chlorallyl enol **8** which was easily cyclized to the corresponding 1,6-dimethylfuro[3,2-*f*]-quinoline-2-one (**9**) in



Scheme 3



Scheme 4



Scheme 5

80% yield when treated with 20% alcoholic potassium hydroxide for 3 h (Scheme 4). The second approach to the synthesis of furo[3,2-*f*]quinoline-2-ones **11d**,**e** made use of the allylic ethers **3d**,**e** of 6-hydroxy-1-methylquinolin-2(1*H*)-one (**1**). The allylic ethers **3d**,**e** were heated in refluxing N,N-diethylaniline for 12 h to give 5-allyl-6-hydroxy-1-methylquinolin-2(1*H*)-one derivatives **10d**,**e** in 65–70% yield. These were then cyclized by stirring with concentrated sulfuric acid [8] at 0–5°C for 3 h to give **11d**,**e** in 75–80% yield. These products failed to undergo dehydrogenation upon treatment with palladized charcoal in boiling diphenyl ether for 3 h (Scheme 5).

It may be concluded that the method described here is simple and general. 6-Propynyloxy-quinolin-2(1*H*)-ones were thermally cyclized regioselectively to pyrano[3,2-*f*]quinolin-2(7*H*)-ones in excellent yields. 6-Allyloxy- and 6-(2-chloroallyloxy)-quinolin-2(1*H*)-ones were thermally rearranged and subsequently cyclized by acid and alcoholic KOH to give regioselectivity the furo[3,2-*f*]-quinolin-2-ones.

Experimental

Melting points are uncorrected. UV/Vis spectra were recorded on a Hitachi 200-20 spectrophotometer (absolute ethanol). IR spectra were run as KBr discs on a Perkin-Elmer 1330 apparatus. ^{1}II NMR spectra were measured in $CDCl_3$ and *DMSO*-d_6 with *TMS* as internal standard on a 300 MHz NMR spectrometer (Bruker). Elemental analyses data were in accordance with the calculated values. Mass spectra were recorded by RSIC (CDRI), Lucknow, India. Silicagel (60–120) was obtained from Spectrochem. Extracts were dried over anhydrous Na_2SO_4.

General procedure for the alkylation of 6-hydroxy-1-methylquinolin-2(1H)-one

6-Hydroxy-1-methylquinolin-2(1*H*)-one (**1**, 1.7 g, 10 mmol) was refluxed with the corresponding alkyl halide (**2**, 10 mmol) in 100 cm^3 dry acetone in the presence of 2 g anhydrous K_2CO_3 for 10–12 h. The reaction mixture was then filtered, and the residue was washed with acetone (3×25 cm^3).

The solvent was removed, and the residual crude mass was purified by column chromatography over silica gel using benzene-ethyl acetate (3:1) as the eluent.

1-Methyl-6-(prop-2-ynyloxy)-quinolin-2-one (**3a**; $C_{13}H_{11}NO_2$)

Yield: 75%; m.p.: 160°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 7.55 (d, $J = 9.5$ Hz, 1H), 7.25 (d, $J = 9.5$ Hz, 1H), 7.18 (dd, $J = 9.5, 3$ Hz, 1H), 7.05 (d, $J = 3$ Hz, 1H), 6.68 (d, $J = 9.5$ Hz, 1H), 4.68 (d, $J = 2.4$ Hz, 2H), 3.64 (s, 3H), 2.48 (t, $J = 2.4$ Hz, 1H) ppm; IR (KBr): $\nu = 2125$, 1640 (CO), 1250 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 234$ (109648), 271 (14791), 352 (15488) nm; MS: $m/z = 213$ (M^+).

1-Methyl-6-(1-methylprop-2-ynyloxy)-quinolin-2-one (**3b**; $C_{14}H_{13}NO_2$)

Yield: 70%; m.p.: 162°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 7.62 (d, $J = 9.5$ Hz, 1H), 7.31 (d, $J = 9.5$ Hz, 1H), 7.26 (dd, $J = 9.5, 3$ Hz, 1H), 7.17 (d, $J = 3$ Hz, 1H), 6.72 (d, $J = 9.5$ Hz, 1H), 4.90 (dq, $J = 6.5, 2$ Hz, 1H), 3.69 (s, 3H), 2.49 (d, $J = 2$ Hz, 1H) 1.70 (d, $J = 6.5$ Hz, 3H) ppm; IR (KBr): $\nu = 1630$, 1255 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 234$ (138038), 271 (19952), 352 (19055) nm; MS: $m/z = 227$ (M^+).

6-(2-Chloroprop-2-enyloxy)-1-methylquinolin-2-one (**3c**; $C_{13}H_{12}ClNO_2$)

Yield: 75%; viscous liquid; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 7.61 (d, $J = 9.5$ Hz, 1H), 7.32 (d, $J = 9.5$ Hz, 1H), 7.23 (dd, $J = 9.5, 3$ Hz, 1H), 7.04 (d, $J = 3$ Hz, 1H), 6.73 (d, $J = 9.5$ Hz, 1H), 5.57 (s, 1H), 5.47 (s, 1H), 4.64 (s, 2H), 3.71 (s, 3H) ppm; IR (KBr): $\nu = 1620$, 1255 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 234$ (95499), 271 (13804), 352 (13490) nm; MS: $m/z = 251, 249$ (M^+).

1-Methyl-6-(prop-2-enyloxy)-quinolin-2-one (**3d**; $C_{13}H_{13}NO_2$)

Yield: 70%; m.p.: 115°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 7.55 (d, $J = 9.5$ Hz, 1H), 7.25 (d, $J = 9.5$ Hz, 1H), 7.15 (dd, $J = 9.5, 3$ Hz, 1H), 6.97 (d, $J = 3$ Hz, 1H), 6.68 (d, $J = 9.5$ Hz, 1H), 6.06 (m, 1H), 5.35 (m, 2H), 4.54 (m, 2H), 3.66 (s, 3H) ppm; IR (KBr): $\nu = 1630$, 1240 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 234$ (141254), 272 (23442), 353 (21878) nm; MS: $m/z = 215$ (M^+).

6-(But-2-enyloxy)-1-methylquinolin-2-one (**3e**; $C_{14}H_{15}NO_2$)

Yield: 75%; viscous liquid; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 7.60 (d, $J = 9.5$ Hz, 1H), 7.27 (d, $J = 9.5$ Hz, 1H), 7.20 (dd, $J = 9.5, 3$ Hz, 1H), 7.01 (d, $J = 3$ Hz, 1H), 6.72 (d, $J = 9.5$ Hz, 1H), 5.82 (m, 2H), 4.51 (d, $J = 6$ Hz, 2H), 3.71 (s, 3H), 1.77 (d, $J = 6.5$ Hz, 3H), ppm; IR (KBr): $\nu = 1640$, 1250 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 215$ (83176), 234 (169824), 280 (23988) 354 (25119) nm; MS: $m/z = 229$ (M^+).

General procedure for the rearrangement of compounds **3a–e**

Compounds **3a–e** (3 mmol) were refluxed in 4 cm^3 N,N-diethylaniline for 12 h. The reaction mixture was cooled and poured into an ice cold 1:1 HCl solution. The solution was then extractd with 3×25 cm^3 $CHCl_3$. The $CHCl_3$ extract was washed with 3×25 cm^3 1:1 HCl, 3×25 cm^3 H_2O, and dried (Na_2SO_4). The $CHCl_3$ was removed, and the crude mass was then purified by column chromatography over silica gel using benzene-ethyl acetate (3:1) as the eluent.

1-Methylpyrano[3,2-f]quinolin-2(7H)-one (**4a**; $C_{13}H_{11}NO_2$)

Yield: 65%; viscous liquid; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 7.96 (d, $J = 9.5$ Hz, 1H), 7.26 (d, $J = 9.5$ Hz, 1H), 7.17 (d, $J = 9.5$ Hz, 1H), 7.01 (d, $J = 10$ Hz, 1H), 6.84 (d, $J = 9.5$ Hz, 1H), 6.12 (dt,

$J = 10, 3.9$ Hz, 1H), 4.91 (dd, $J = 3.9, 1.5$ Hz, 2H), 3.79 (s, 3H) ppm; IR (KBr): $\nu = 1635$, 1240 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 235$ (123027), 286 (36308), 363 (22909) nm; MS: $m/z = 213$ (M^+).

1,7-Dimethylpyrano[3,2-f]quinolin-2(7H)-one (**4b**; $C_{14}H_{13}NO_2$)

Yield: 60%; viscous liquid; ^1H NMR ($CDCl_3$, δ, 300 MHz): 7.88 (d, $J = 9.5$ Hz, 1H), 7.27 (d, $J = 9.5$ Hz, 1H), 7.17 (d, $J = 9.5$ Hz, 1H), 7.09 (d, $J = 10$ Hz, 1H), 6.87 (d, $J = 9.5$ Hz, 1H), 5.89 (m, 1H), 4.21 (m, 1H), 3.71 (s, 3H), 2.19 (d, $J = 4$ Hz, 3H) ppm; IR (KBr): $\nu = 1645$, 1250 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 235$ (194984), 338 (32359) nm; MS: $m/z = 227$ (M^+).

5-(2-Chloroprop-2-enyl)-6-hydroxy-1-methylquinolin-2-one (**8**; $C_{13}H_{12}ClNO_2$)

Yield: 65%; m.p.: 230°C; ^1H NMR (*DMSO*-d_6, δ, 300 MHz): 9.67 (s, 1H), 7.91 (d, $J = 9.5$ Hz, 1H), 7.37 (d, $J = 9.5$ Hz, 1H), 7.21 (d, $J = 9.5$ Hz, 1H), 6.61 (d, $J = 9.5$ Hz, 1H), 5.20 (s, 1H), 4.91 (s, 1H), 3.95 (s, 2H), 3.59 (s, 3H) ppm; IR (KBr): $\nu = 3060$, 1630 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 215$ (144544), 235 (169824), 281 (48978), 363 (33113) nm; MS: $m/z = 251, 249$ (M^+).

6-Hydroxy-1-methyl-5-(prop-2-enyl)-quinolin-2-one (**10d**; $C_{13}H_{13}NO_2$)

Yield: 70%; m.p.: 234°C; ^1H NMR (*DMSO*-d_6, δ, 300 MHz): 9.46 (s, 1H), 7.93 (d, $J = 9.5$ Hz, 1H), 7.29 (d, $J = 9.5$ Hz, 1H), 7.17 (d, $J = 9.5$ Hz, 1H), 6.57 (d, $J = 9.5$ Hz, 1H), 5.91 (m, 1H), 4.93 (m, 2H), 3.64 (d, $J = 5.6$ Hz, 2H), 3.57 (s, 3H), ppm; IR (KBr): $\nu = 3050$, 1630 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 215$ (162181), 236 (177828), 284 (56234), 353 (33884) nm; MS: $m/z = 215$ (M^+).

6-Hydroxy-1-methyl-5-(1-methylprop-2-enyl)-quinolin-2-one (**10e**; $C_{14}H_{15}NO_2$)

Yield: 65%; m.p.: 235°C; ^1H NMR (*DMSO*-d_6, δ, 300 MHz): 9.48 (s, 1H), 8.11 (d, $J = 9.5$ Hz, 1H), 7.29 (d, $J = 9.5$ Hz, 1H), 7.17 (d, $J = 9.5$ Hz, 1H), 6.53 (d, $J = 9.5$ Hz, 1H), 6.25 (m, 1H), 5.05 (m, 2H), 4.35 (m, 1H), 3.57 (s, 3H), 1.42 (d, $J = 7.2$ Hz, 3H) ppm; IR (KBr): $\nu = 3080$, 1632 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 215$ (131826), 236 (131826), 283 (42658), 363 (26303) nm; MS: $m/z = 229$ (M^+).

1,6-Dimethylfuro[3,2-f]quinolin-2-one (**9**, $C_{13}H_{11}NO_2$)

Compound **8** (250 mg, 1 mmol) was refluxed in 3 cm^3 20% ethanolic KOH for 3 h. The solvent was removed, and the residue was extracted with 3×20 cm^3 $CHCl_3$. The combined extract was washed with 3×20 cm^3 H_2O and dried (Na_2SO_4). After removal of the solvent, the crude mass was purified by column chromatography over silica gel using benzene-ethyl acetate (3:1) as the eluent.

Yield: 80%; m.p.: 172°C; ^1H NMR ($CDCl_3$, δ, 300 MHz): 7.93 (d, $J = 9.5$ Hz, 1H), 7.61 (d, $J = 9.5$ Hz, 1H), 7.22 (d, $J = 9.5$ Hz, 1H), 6.79 (d, $J = 9.5$ Hz, 1H), 6.68 (s, 1H), 3.79 (s, 3H), 2.53 (s, 3H) ppm; IR (KBr): $\nu = 1640$, 1265 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 221$ (60256), 317 (24547) nm; MS: $m/z = 213$ (M^+).

Cyclization of compounds **10d,e**

Compounds **10d,e** (1 mmol) were dissolved in 3 cm^3 conc. H_2SO_4 at 0–5°C and stirred for 3 h. The mixture was poured into ice-water, neutralized with Na_2CO_3, and extracted with 3×20 cm^3 $CHCl_3$. The combined extract was washed with 3×20 cm^3 H_2O and dried (Na_2SO_4). The solvent was removed, and the crude mass was purified by column chromatography over silica gel using benzene-ethyl acetate (3:1) as the eluent.

5,6-Dihydro-1,6-dimethylfuro[3,2-f]quinolin-2-one (**11d**, $C_{13}H_{13}NO_2$)

Yield: 80%; m.p.: 190°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 7.53 (d, $J = 9.5$ Hz, 1H), 7.15 (d, $J = 9.5$ Hz, 1H), 7.02 (d, $J = 9.5$ Hz, 1H), 6.73 (d, $J = 9.5$ Hz, 1H), 5.08 (m, 1H), 3.70 (s, 3H), 3.52 (dd, $J = 15.6, 8.9$ Hz, 1H), 2.99 (dd, $J = 15.6, 7.5$ Hz, 1H), 1.52 (d, $J = 6.5$ Hz, 3H) ppm; IR (KBr): $\nu = 1640$, 1250 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 216$ (131826), 238 (165959), 284 (51286), 372 (26915) nm; MS: $m/z = 215$ (M^+).

5,6-Dihydro-1,5,6-trimethylfuro[3,2-f]quinolin-2-one (**11e**, $C_{14}H_{15}NO_2$)

Yield: 75%; viscous liquid; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 7.65 (d, $J = 9.5$ Hz, 1H), 7.15 (d, $J = 9.5$ Hz, 1H), 7.03 (d, $J = 9.5$ Hz, 1H), 6.74 (d, $J = 9.5$ Hz, 1H), 4.90 (quintet, $J = 6.5$ Hz, 1H), 3.71 (s, 3H), 3.55 (quintet, $J = 7.2$ Hz, 1H), 1.52 (d, $J = 6.5$ Hz, 3H), 1.19 (d, $J = 7.2$ Hz, 3H) ppm; IR (KBr): $\nu = 1650$, 1260 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 215$ (144544), 238 (181970), 283 (60256), 371 (33113) nm; MS: $m/z = 229$ (M^+).

Attempted dehydrogenation of compound **11d,e**

Compound **11d,e** (0.5 mmol) was refluxed with 25 mg 10% Pd/C in 4 cm^3 diphenyl ether for 3 h. No change was observed as evidenced from TLC of the reaction mixture, co-TLC with an authentic sample of **11**, and an IR spectrum superimposable with that of starting material.

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