Synthesis of 4-Cyanofuro(2,3-b)quinolines

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2-Chloro-4-cyano-3-vinylquinolines, 4-Cyano-3-vinylquinoline-2-ones, 4-Cyanofuro(2,3-b)quinolines

Synthesis of 4-cyanofuro(2,3-b)quinolines starting from 2-chloro-4-cyano-3-vinylquinolines is described.

The furoquinoline alkaloids [1] which have been isolated from numerous plants of the Rutaceae are derivatives of the furo(2,3-b)quinoline system (1). Considerable efforts have been expended in this laboratory towards the realization of synthetic schemes which could allow the facile preparation of 1 in myriad varieties including the naturally occurring derivatives. The fait accompli of our investigative efforts were the synthesis of 1 in different substitution patterns by way of appropriately substituted 2-quinolone-3-acetic acids [2, 3] and 3-vinyl-2-quinolones [4–6]. Our subsequent interest was to obtain the hitherto unknown 4-cyanofuro(2,3-b)quinolines (4) and study their properties in relation to those of 9-cyanoacridines [7].

The precursors for our synthetic scheme were 4-cyano-3-vinylquinolin-2-ones (3) which were easily derived by hydroxy-dechlorination of 2-chloro-4-cyano-3-vinylquinolines (2) [8] using glacial acetic acid. Addition of bromine across the vinyl bond in 3 followed by heating the resulting bromine-adduct with triethyl amine in chloroform gave 4 in 50–70% yield. Hydrogenation of 4a over palladized-charcoal in ethanol gave the dihydrofuroquinoline 5.

5 was also derived by an alternative sequence starting with 2-chloro-3-(2-hydroxyethyl)quinoline-4-carboxamide (6) which on treatment with phosphorus oxychloride gave the dichloro-compound 7. On heating with 5% hydrochloric acid in dioxan, 7 readily underwent hydroxy-dechlorination to furnish 8 from which 5 was obtained by cyclo-dehydrochlorination with silver oxide in aqueous ethanol. When 3a was subjected to Prevost’s reaction it gave 3-acetoxy-2,3-dihydro-4-cyanofuro-(2,3-b)quinoline (9). When reacted with methanol solution containing bromine, 3a gave the methoxy derivative 10.
Experimental

Melting points were determined on a Boetius microheating table and are uncorrected. IR spectra were recorded on Perkin-Elmer 597 spectrophotometer and $^1H$ NMR spectra on a Hitachi R-600 spectrometer using TMS as internal standard.

4-Cyano-3-vinylquinolin-2(1H)ones (3)

The quinolones 3a, 3b, 3c and 3d were obtained respectively from the chloroquinolines 2a, 2b, 2c and 2d (0.002 mol) by heating with glacial acetic acid (20 ml) at 125°C for 2 h. The reaction mixture was cooled and poured into ice-water. The precipitated solid was collected, washed with benzene and recrystallized from a suitable solvent.

3a: Yield 70%, m.p. > 300°C (EtOH). - IR (KBr): 2930 (N-H), 2200 (CN), 1660 (N-HCO) cm$^{-1}$.

Calcd C 73.46 H 4.08%,

Found C 73.57 H 4.19%.

3b: Yield 69%, m.p. 280°C (dec) (acetonitrile). - IR (KBr): 2975 (N-H), 2200 (CN), 1640 (N-HCO) cm$^{-1}$.

Calcd C 74.29 H 4.86%,

Found C 74.50 H 4.76%.

3c: Yield 76%; m.p. 290°C (dec) (acetic acid).

- IR (KBr): 2975 (N-H), 2200 (CN), 1650 (N-HCO) cm$^{-1}$.

Calcd C 62.66 H 3.04%,

Found C 62.66 H 3.20%.

3d: Yield 65%; m.p. 190°C (dec) (acetonitrile).

- IR (KBr): 2960 (N-H), 2200 (CN), 1650 (N-HCO) cm$^{-1}$.

Calcd C 52.58 H 2.55%,

Found C 52.56 H 2.71%.

4-Cyanofuro(2,3-b)quinolines (4)

A chloroform solution (10 ml) containing 160 mg (0.001 mole) of bromine was added slowly to the quinolone 3 (0.001 mole) in chloroform (30 ml) kept stirred and cooled. After the addition was over, it was kept aside for 1 h. Thereafter it was mixed with triethylamine (9 ml) and the resulting mixture was heated at reflux for 3 h cooled and filtered to remove triethylammonium bromide. Evaporation of the filtrate under diminished pressure gave a residue which was chromatographed over basic alumina using benzene as the eluent. The product obtained was recrystallized from pet.ether (60–80°C)/benzene.

4a: Yield 70%, m.p. 185–186°C. - IR (KBr): 2200 cm$^{-1}$ (CN). - $^1H$ NMR (CDCl$_3$): δ = 7.15 (d, 1H, C$_3$–H), 7.70 (d, 1H, C$_2$–H), 7.76–8.45 (m, 4H, H-Arom.) ppm.

Calcd C 74.27 H 3.10%,

Found C 74.22 H 2.90%.

4b: Yield 65%; m.p. 208–209°C. - IR (KBr): 2200 cm$^{-1}$ (CN). - $^1H$ NMR (CDCl$_3$): δ = 2.6 (s, 3H, -CH$_3$), 7.11 (d, 1H, C$_3$–H), 7.55 (d, 1H, C$_2$–H), 7.71–8.02 (m, 2H, C$_7$–H and C$_8$–H), 8.20 (s, 1H, C$_5$–H) ppm.

Calcd C 75.00 H 3.85%,

Found C 74.90 H 3.94%.

4c: Yield 60%; m.p. 215–216°C. - IR (KBr): 2200 cm$^{-1}$ (CN). - $^1H$ NMR (CDCl$_3$): δ = 7.15 (d, 1H, C$_3$–H), 7.71 (d, 1H, C$_2$–H), 7.79–8.06 (m, 2H, C$_7$–H and C$_8$–H), 8.22 (s, 1H, C$_5$–H) ppm.

Calcd C 63.24 H 2.29%,

Found C 63.02 H 2.19%.

4d: Yield 45%; m.p. 239–240°C. - IR (KBr): 2200 cm$^{-1}$ (CN). - $^1H$ NMR (CDCl$_3$): δ = 7.15 (d, 1H, C$_3$–H), 7.81 (d, 1H, C$_2$–H), 7.91–8.06 (m, 2H, C$_7$–H and C$_8$–H), 8.47 (s, 1H, C$_5$–H) ppm.

Calcd C 52.74 H 1.83%,

Found C 52.95 H 1.97%.

Hydrogenation of 4a to 5

To a solution of 4a (0.100 g) in methanol (100 ml) was added 80 mg of 5% palladized charcoal and shaken over hydrogen (50 lbs) in a Parr-hydrogenator. After filtering off the catalyst, the solvent was evaporated to give a residue which was then chromatographed over neutral alumina to furnish 5.

Yield 79%; m.p. 198–199°C (Pet.ether/benzene). - IR (KBr): 2210 cm$^{-1}$ (CN). - $^1H$ NMR (CDCl$_3$): δ = 3.58 (t, 2H, C$_3$–H), 4.79 (t, 2H, C$_2$–H), 7.42–8.10 (m, 4H, H-Arom.).

Synthesis of 7

A mixture of 6 (0.5 g) and phosphorous oxychloride (5 ml) was heated at 110°C for 2 h. The reaction mixture was cooled, poured into ice-water, neutralized with ammonia solution and ex-
tracted with chloroform. The extract was dried over anhydrous magnesium sulphate and then evaporated to give a residue. The residue was placed over a column of alumina (neutral) and eluted with pet.ether (60–80 °C) when 7 after evaporation of the solvent was obtained as colourless needles.

Yield 0.325 g (65%); m.p. 101–102 °C. - IR (KBr): 2205 cm⁻¹ (CN), 'H NMR (CDCl₃): δ = 3.32–4.10 (m, 4 H, CH₂–CH₂), 7.6–8.24 (m, 4 H, H-Arom.). - Mass: M⁺: 251.

Further elution of the column with pet.ether (60–80 °C)/benzene furnished a product (yield 25%, m.p. 132–133 °C) identified to be 3,4-dihydro-5-chloropyrano(4,3-c)quinolin-1(1H)-one [9].

Conversion of 7 to 8

A mixture of 7 (0.360 g), 6 N hydrochloric acid (9 ml) and dioxan (7 ml) was refluxed for 3 h and thereafter the solvent was evaporated under vacuum to give a residue. The residue was digested with water (10 ml) and filtered. The solid was recrystallized from alcohol when 8 was obtained as colourless crystals.

Yield 0.3 g (90%); m.p. 208–210 °C. - IR (KBr): 2900 (NH), 1650 (CO) cm⁻¹. - Mass: M⁺: 232.

C₁₂H₈N₂Cl₂
Calcd C 57.37 H 3.19%,
Found C 57.53 H 3.35%.

Acetoxy cyclization of 3a

The vinylquinolone 3a (0.002 mole) was dissolved in glacial acetic acid (15 ml) and silver acetate (0.0045 mole) was added. Well powdered iodine (0.002 mole) was then added in small portions to the stirred reaction mixture over a period of 1 h at room temperature. After stirring for an hour more, the precipitated silver iodide was removed by filtration and washed with chloroform. The filtrate and the washings were combined, diluted with water and extracted with chloroform. The extract was washed with water containing a little thiosulphate and dried over anhydrous sodium sulphate. The solvent was removed, the residue was placed over a column of alumina and eluted with benzene. The dihydrofuroquinoline was obtained as colourless crystals on crystallization from pet.ether (60–80 °C)/benzene.

Yield 0.355 g (70%); m.p. 123–124 °C. - IR (KBr): 2200 (CN), 1700 (OOC₂H₅) cm⁻¹. - Mass: M⁺: 254.

C₁₄H₁₀N₂O₃
Calcd C 66.14 H 3.93%,
Found C 65.99 H 3.81%.

Methoxy cyclization of 3a

A methanol solution (10 ml) containing 160 mg (0.001 mole) of bromine was added slowly to the quinolone 3a (0.001 mole) in methanol (20 ml). It was kept aside for 1 h. Thereafter it was mixed with triethylamine (4 ml) and the resulting mixture was heated at reflux for 3 h, cooled, and filtered. Evaporation of the filtrate under diminished pressure gave a residue which was chromatographed over basic alumina using benzene as eluent. The product obtained was recrystallized from pet.ether (60–80 °C)/benzene.

Yield 74%; m.p. 156–157 °C. - IR (KBr): 2220 cm⁻¹ (CN). - 'H NMR (CDCl₃): δ = 3.6 (s, 3 H, –OCH₃), 4.7 (d, 2 H, C₂–H), 5.35 (t, 1 H, C₃–H), 7.6–8.2 (m, 4 H, H-Arom.).


