

Synthesis of Pyranoquinoline alkaloids *via* (4+2) cycloaddition reaction

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Abstract

An easy route to synthesize pyranoquinoline based alkaloids like flindersine, haplamine, *N*-methylflindersine and its derivatives were performed from the respective 4-hydroxyquinolin-2(1*H*)-one, dimethyl acrylic acid and para formaldehyde through generation of *O*-quinone methide intermediates and subjecting (4+2) cycloaddition. Further, dihydro intermediates were oxidized by DDQ.

Introduction

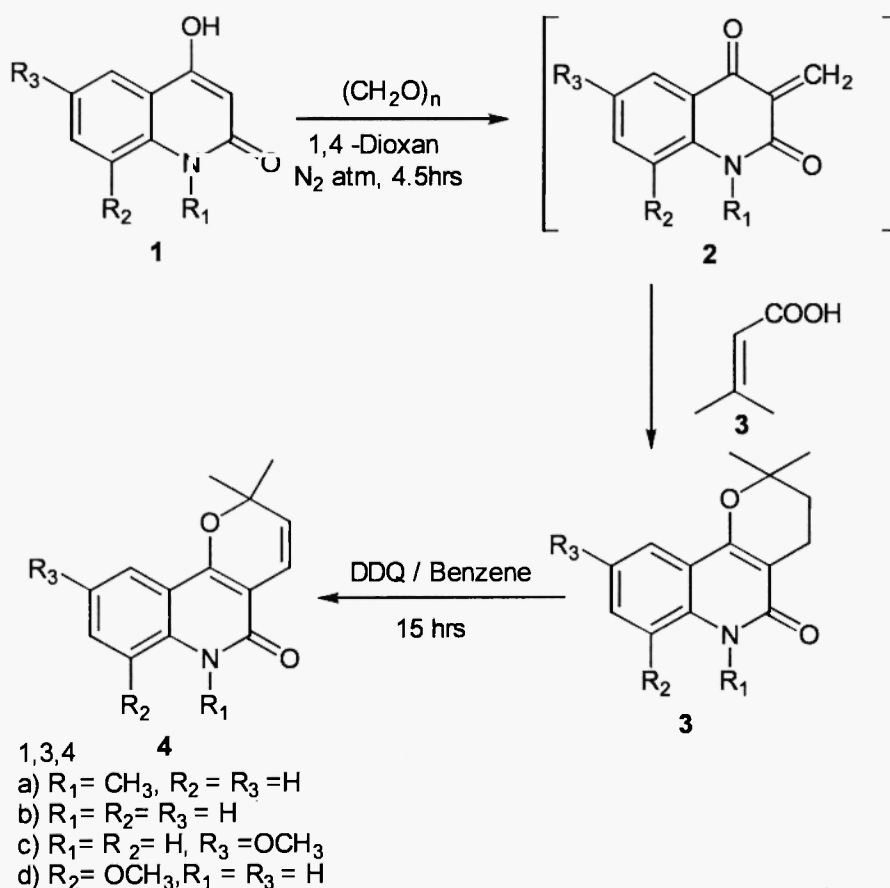
Pyranoquinolines are the main constituent unit of the many of the alkaloids of the plant family Rutaceae and have gained much importance because of their interesting pharmacological properties¹⁻³. Flindersine **4a**, a member of a family of pyranoquinoline alkaloids, was isolated from the wood of flindersia australis in 1984⁴. *O*-Quinone methide are important intermediates in organic synthesis and their role as 1,3-oxabutadiene unit in inverse electron demand Diels-Alder reactions has been extensively studied⁵⁻⁷. However the Diels-Alder reactions of heterocyclic quinone methides in general, and quinolone quinone methide in particular, have received only scarce attention⁸⁻¹⁰.

In this paper we have scripted a novel straight forward method for the synthesis of pyranoquinoline alkaloids like flindersine, haplamine, *N*-methylflindersine and its derivative's from 2,4-dihydroxy quinoline, para formaldehyde with 3,3-dimethylacrylic acid as an electron rich diene. It preferentially undergoes an inverse electron demand cycloaddition reaction^{11,5} leading to the formation of pyranoquinoline alkaloids.

Results and Discussion

As a first step, 4-hydroxy-2(1*H*)-quinoline and its derivatives (**1a-d**) was prepared from reported procedure [12,13]. Generation of the required 3-methylene-quinolin-2,4 (1*H*, 3*H*)-diones (**2a-d**) was made by refluxing a solution of **1a-d** with para - formaldehyde in 1,4 - dioxane. To the refluxing solution, 3,3-dimethylacrylic acid was added and refluxed under nitrogen atmosphere for 4.5 hours, to afford the dihydroproduct **3a-d**, and further it was oxidized by DDQ in benzene to form a respective pyranoquinolines (**4 a-d**). (Scheme I)

Scheme I



In conclusion, we have proposed a convenient method for the synthesis of pyranoquinoline alkaloids *via* inverse electron demand Diels-Alder reaction of quinone methide, the latter being generated *in situ* by a simple and effective means, since pyranoquinolines constitute a large group of naturally occurring¹⁴ biologically active compounds¹⁵ and they have potential medicinal¹⁵ and synthetic¹⁶ applications. The present procedure could also eliminate

tediousness involved in the earlier method⁹ of generation of quinolone quinone methide, time consumption and requires only meager usage of DDQ at later stage.

Experimental

Thin layer chromatography was used to access the progress of the reaction and purity of products. Melting Points were determined on a Boetius Microheating Table (Japan) and Mettler-FP5 Melting apparatus and are uncorrected. IR spectra were recorded in Shimadzu-8201 FT instrument (Japan) in KBr disc and only noteworthy absorption levels (reciprocal centimeter) are listed. ¹H-NMR spectra were recorded in AMX-400MHz (US) and Bruker-300MHz spectrometer in CDCl₃ solution; Chemical shifts are expressed in ppm (δ) relative TMS. Satisfactory microanalyses were obtained on Carlo Erba 1106 and Perkin Elmer models 240 CHN analyzer(UK). Mass spectra were recorded on a Jeol-300 mass spectrometer(70eV) (Japan). Chemicals such as DDQ and 3,3-dimethylacrylic acid were purchased directly from Aldrich Company.

Typical Procedure

Synthesis of dihydropyranoquinoline alkaloids: Equal moles of 4-hydroxy-1-methylquinolin-2(1*H*)-one (0.001mol) (**1a**) and 3,3-dimethylacrylic acid (0.001mol) with paraformaldehyde (0.008mol) in dry 1,4-dioxan were heated at 120 °C under nitrogen atmosphere for 4.5 hrs. After completion of reaction, 1,4-dioxan was distilled off and the crude reaction mixture was extracted with ethyl acetate. The organic layer was washed successively using saturated aq. sodium carbonate solution (2x 20 mL) and then brine and dried over sodium sulphate and concentrated. Column chromatography (silica gel 60-120 mesh) of the product using a gradient mixture of petroleum ether and ethylacetate afforded dihydroproduct (**3a**). Same procedure was also applied for its derivatives **3b-d**.

Synthesis of flindersine and its analogues: Equal moles of respective dihydro pyranoquinolines (**3a-d**) (0.001 mol), and DDQ (0.001 mol) in 50 mL of benzene were refluxed for 15 hrs. After cooling, the reaction mixture was filtered and the solvent was evaporated. The residual mass was

extracted with ethyl acetate. The combined organic extracts when subjected to silica gel column chromatography (pet.ether/EtOAc) gave the desired products (**4a-d**).

2,2,6-Trimethyl-3,4-dihydropyrano[3,2-c]quinolin-5-one (3a): mp 147 °C; yield 80%; IR (KBr, γ_{\max}) cm^{-1} 1643 cm^{-1} (C=O); ^1H NMR (CDCl_3) δ 0.85 (t, 2H, $\text{C}_3\text{-CH}_2$, $J=4.86\text{Hz}$), δ 1.28 (t, 2H, $\text{C}_4\text{-CH}_2$, $J=4.86\text{Hz}$), δ 1.4 (s, 6H, $2\times\text{CH}_3$), δ 3.8 (s, 3H, N-CH_3), δ 7.1-8.2 (m, 4H, Ar-H); MS (m/z) 243; CHN Analysis (%): Calcd. C 74.05, H 7.04, N 5.76; Found C 74.41, H 7.22, N 5.98 ($\text{C}_{15}\text{H}_{17}\text{NO}_2$).

2,2-Dimethyl-3,4-dihydropyrano[3,2-c]quinolin-5(6H)-one (3b): mp 207 °C; Yield 82%; IR (KBr, γ_{\max}) cm^{-1} 1641, 3240-3360, ^1H NMR (CDCl_3) δ 1.0 (t, 2H, $\text{C}_3\text{-CH}_2$, $J=5.12\text{Hz}$), δ 1.35 (s, 6H, $2\times\text{CH}_3$), δ 1.7 (t, 2H, $\text{C}_4\text{-CH}_2$, $J=5.12\text{Hz}$), δ 6.9-7.5 (m, 4H, Ar-H), δ 11.4 (s, 1H, NH); MS (m/z) 229; CHN Analysis (%): Calcd. C 73.34, H 6.59, N 6.11; Found C 73.32, H 6.05, N 6.05 ($\text{C}_{14}\text{H}_{15}\text{NO}_2$).

9-Methoxy-2,2-dimethyl-3,4-dihydropyrano[3,2-c]quinolin-5(6H)-one (3c): mp 233 °C; Yield 63%; IR (KBr, γ_{\max}) cm^{-1} 1668, 3410; ^1H NMR (CDCl_3) δ 0.9 (t, 2H, $\text{C}_3\text{-CH}_2$, $J=5.04\text{Hz}$), δ 1.39 (s, 6H, $2\times\text{CH}_3$), δ 1.5 (t, 2H, $\text{C}_4\text{-CH}_2$, $J=5.04\text{Hz}$), δ 3.8 (s, 3H, $-\text{OCH}_3$), δ 6.9-7.6 (m, 3H, Ar-H), δ 10.4 (bs, 1H, NH); MS (m/z) 259; CHN Analysis (%): Calcd. C 69.48, H 6.61, N 5.40; Found C 70.23, H 6.65, N 5.44 ($\text{C}_{15}\text{H}_{17}\text{NO}_3$).

7-Methoxy-2,2-dimethyl-3,4-dihydropyrano[3,2-c]quinolin-5(6H)-one (3d): mp 211 °C; Yield 61%; IR (KBr, γ_{\max}) cm^{-1} 1652, 3230; ^1H NMR (CDCl_3) δ 1.25 (t, 2H, $\text{C}_3\text{-CH}_2$, $J=5.45\text{Hz}$), δ 1.6 (s, 6H, $2\times\text{CH}_3$), δ 1.8 (t, 2H, $\text{C}_4\text{-CH}_2$, $J=5.45\text{Hz}$), δ 3.8 (s, 3H, $-\text{OCH}_3$), δ 6.6-7.7 (m, 3H, Ar-H), δ 10.15 (bs, 1H, NH); MS (m/z) 259; CHN Analysis (%): Calcd. C 69.48, H 6.61, N 5.40; Found C 70.04, H 6.56, N 5.60 ($\text{C}_{15}\text{H}_{17}\text{NO}_3$).

N-Methylflindersine (4a): mp 85 °C; Yield 85%; IR (KBr, γ_{\max}) cm^{-1} 1652, 2913; ^1H NMR (CDCl_3) δ 1.45 (s, 6H, $2\times\text{CH}_3$), δ 3.6 (s, 3H, N-CH_3), δ 5.8 (d, 1H, $\text{C}_3\text{-H}$, $J=6.23\text{Hz}$), δ 6.9-

7.8 (m, 5H, Ar-H & C₄-H); MS (m/z) 241 ; CHN Analysis (%): Calcd. C 74.67, H 6.27, N 5.80; Found C 74.41, H 6.22, N 5.96 (C₁₅H₁₅NO₂).

Flindersine (4b): mp 195 °C; Yield 90%; IR (KBr, γ_{\max}) cm⁻¹ 1648, 3240; ¹H NMR (CDCl₃) δ 1.35 (s, 6H, 2 x CH₃), δ 5.3 (d, 1H, C₃-H, J = 5.67Hz), δ 6.6-7.4 (m, 5H, Ar-H & C₄-H), δ 11.4 (s, 1H, NH); MS (m/z) 227 ; CHN Analysis (%): Calcd. C 73.99, H 5.77, N 6.16; Found C 73.32, H 5.88, N 6.05 (C₁₄H₁₃NO₂).

Haplamine (4c): mp 210 °C; Yield 90%; IR (KBr, γ_{\max}) cm⁻¹ 1648, 3210; ¹H NMR (CDCl₃) δ 1.39 (s, 6H, 2 x CH₃), δ 3.8 (s, 3H, -OCH₃), δ 5.8 (d, 1H, C₃-H, J =7.32Hz), δ 6.9-7.8 (m, 4H, Ar-H & C₄-H), δ 10.1 (bs, 1H, NH); MS (m/z) 257 ; CHN Analysis (%): Calcd. C 70.02, H 5.88, N 5.44; Found C 70.23, H 5.65, N 5.44 (C₁₅H₁₅NO₃).

7-Methoxyflindersine (4d): mp 178 °C; Yield 65%; IR (KBr, γ_{\max}) cm⁻¹ 1665, 3065; ¹H NMR (CDCl₃) δ 1.5 (s, 6H, 2 x CH₃), δ 3.9 (s, 3H, -OCH₃), δ 5.8 (d, 1H, C₃-H, J =5.46Hz), δ 6.9-7.6 (m, 4H, Ar-H & C₄-H), δ 10.9 (s, 1H, NH); MS (m/z) 257 ; CHN Analysis (%): Calcd. C 70.02, H 5.88, N 5.44; Found C 70.14, H 5.56, N 5.60 (C₁₅H₁₅NO₃).

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