A facile synthesis of 7:8 and 6:7-fused pyrano pyrido coumarins

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A simple and highly efficient method for 7:8/6:7-fused pyrano pyrido coumarins 2a-e from 8/6-formyl-7-hydroxy coumarins 1a-e by modified Hantzsch synthesis has been developed.

7:8/6:7-Fused heterocyclic coumarins have variety of biological importance such as photosensitizing in the treatment of vitiligo, psoriasis\(^1\),\(^2\), coronary vasodilator\(^3\), photodynamic\(^4\) and antioxidant\(^5\) activities. Reaction of aldehydes with ethyl 3-aminocrotonate to give dihydropyridines, is called modified Hantzsch synthesis\(^6\). We report here the synthesis of pyrano pyrido coumarins 2a-e by the reaction of 8/6-formyl-7-hydroxy-4-methyl coumarins\(^7\) 1a-e with ethyl 3-aminocrotonate in acetic acid medium.

3-Chloro-8-formyl-7-hydroxy-4-methylcoumarin 1a on treatment with ethyl 3-aminocrotonate in acetic acid at room temperature for 96 h gave 10-carboethoxy-3-chloro-4,9,11-trimethyl[2,3-j]-pyrano[3,2-c]-pyrido[1]-benzopyran[2H,8H]-2,8-dione 2a (Scheme I). Its structure was established from analytical and spectral data. IR spectrum of 2a showed three carbonyl absorptions at 1755 (α-pyran), 1735 (ester) and 1720 (coumarin). \(^1\)H NMR showed signals at δ 4.50 (q, 2H, J=8 Hz, –OCH₂) and 1.45 (t, 3H, J=8 Hz, –CH₃) and two new sp² carbon linked pyrdo methyl groups appeared as a singlet at δ 2.82 and 2.81. The signals at δ 7.82 and 7.38 as AB doublet (J=10 Hz) are due to the C-5 and C-6 aromatic protons, suggesting the pyrano pyrido ring is fused to 7:8 positions of the coumarin. In the \(^13\)C NMR, the newly formed pyridine ring carbons appeared at δ 152.0 (C-8a), 154.0 (C-9), 137.3 (C-10) and 158.8 (C-11) and 161.0 (C-12a) and the pyrano carbonyl appeared at δ 164.7. Its M⁺ is observed at m/z 413 (100%), 415 (M+2, 33%) and other ions are m/z 385 (19%) (M-CO), 368 (37%) (M-OCCH₃), and 340 (21%) (M-COOCCH₃).

Similarly, 10-carboethoxy-4,9,11-trimethyl[2,3-j] pyrano[3,2-c]pyrido[1]-benzopyran[2H,8H]-2,8-dione 2b, 10-carboethoxy-4,6,9,11-tetramethyl[2,3-j]pyrano[3,2-c]pyrido[1]-benzopyran[2H,8H]-2,8-dione 2c, 10-carboethoxy-3,6-dichloro-4,9,11-trimethyl[2,3-j]pyrano[3,2-c]pyrido[1]-benzopyran[2H,8H]-2,8-dione 2d and 8-carboethoxy-4,7,9,12-tetramethyl[2,3-j]pyrano[3,2-c]pyrido[1]-benzopyran[2H,8H]-2,8-dione 2e were obtained by the reaction of corresponding 8/6-formyl-7-hydroxy coumarins 2b-e with ethyl 3-aminocrotonate (Scheme I). The structures were confirmed by their analytical and spectral data.

In the present study we observed the direct formation of pyridines, instead of the dihydropyridines generally formed in a Hantzsch synthesis.\(^7\) The formation of 10-carboethoxy-3-chloro-4,9,11-trimethyl[2,3-j] pyrano[3,2-c]pyrido[1] benzopyran[2H,8H]-2,8-dione 2a considered to proceed as follows: The first step involves the formation of schiff base 3a by reaction between 3-chloro-8-formyl-7-hydroxy-4-methylcoumarin 1a and ethyl 3-aminocrotonate. Michael addition of second mole of ethyl 3-aminocrotonate results in the formation of 4a which gives intermediate...
dihydropyrido coumarin 5a by the loss of ammonia. Dihydropyrido coumarin 5a under atmospheric oxidation conditions oxidised to pyrido coumarin 6a. The 6a undergoes lactonisation giving rise to pyranopyridocoumarin 2a (Scheme II).

**Experimental Section**

Melting points were determined in open capillary sulfuric acid-bath and are uncorrected. IR spectra were recorded on FT-IR Perkin-Elmer 1710 spectrometer and $^1$H NMR (200 MHz) and $^1$C NMR (50.3 MHz) on a Varian Gemini 200 spectrometer using TMS as an internal standard (chemical shifts in δ, ppm). Mass spectra were recorded on UG Micromass 7070 H instrument.

8/6-Formyl-7-hydroxy-4-methylcoumarins 1a-e were synthesised according to the literature procedures.  

3-Chloro-8-formyl-7-hydroxy-4-methylcoumarin 1a: Yield 75%; m.p. 165°C; IR (KBr): 1715 (CO), 1700 (CHO) cm$^{-1}$; $^1$H NMR (CDCl$_3$): δ 2.45 (s, CH$_3$-4), 7.70 (d, J=8 Hz, H-5), 6.90 (d, J=8 Hz, H-6), 10.60 (s, CHO) and 12.20 (OH-7).

8-Formyl-7-hydroxy-4-methylcoumarin 1b: Yield 80%; m.p. 165°C; IR (KBr): 1715 (CO), 1690 (CHO) cm$^{-1}$; $^1$H NMR (CDCl$_3$): δ 6.18 (s, H-3), 2.40 (s, CH$_3$-4), 7.65 (d, J=8 Hz, H-5), 6.85 (d, J=8 Hz, H-6), 10.62 (s, CHO) and 12.20 (OH-7).

8-Formyl-7-hydroxy-4,6-dimethylcoumarin 1c: Yield 80%; m.p. 165°C; IR (KBr): 1718 (CO), 1700 (CHO) cm$^{-1}$; $^1$H NMR (CDCl$_3$): δ 6.20 (s, H-3), 2.40 (s, CH$_3$-4), 7.80 (s, H-5), 2.40 (s, CH$_3$-6), 10.60 (s, CHO) and 12.70 (OH-7).

3,6-Dichloro-8-formyl-7-hydroxy-4-methylcoumarin 1d: Yield 75%; m.p. 203°C; IR (KBr): 1720 (CO), 1695 (CHO) cm$^{-1}$; $^1$H NMR (CDCl$_3$): δ 2.60 (s, CH$_3$-4), 7.80 (s, H-5), 10.60 (s, CHO) and 12.00 (OH-7).

6-Formyl-7-hydroxy-4,8-dimethylcoumarin 1e: Yield 80%; m.p. 220°C; IR (KBr): 1720 (CO), 1692
General procedure for the synthesis of 7/8/6:7-fused pyranopyridocoumarins 2a-e. A solution of 8/6-formyl-7-hydroxy-4-methyl coumarins 1a-e (10 mmole) and ethyl 3-aminocrotonate (20 mmole) in glacial acetic acid was kept at room temperature for 96 hr and diluted to overnight at room temperature. The reaction mixture was extracted with ethyl acetate and washed with 2% NaHCO₃ solution and water. Concentration of ethyl acetate gave 7/8/6,7-fused pyrano pyridocoumarin 2a-e which was recrystallised from chloroform as colourless crystals, yield 90%.

10-Carboethoxy-3-chloro-4,9,11-trimethyl [2,3-]pyrano[3,2-c]pyrido[1]benzo-pyran [2H, 8H]-2,8-dione 2a: m.p. 240°C; IR (KBr): 1720 (CO, coumarin), 1735 (CO, ester), 1730 (CO, α-pyran) cm⁻¹; ¹H NMR (CDCl₃): δ 6.18 (s, H-3), 2.35 (s, CH₃-4), 7.62 (s, H-5), 2.42 (s, CH₃-8), 9.98 (s, CHO) and 11.60 (OH-7).

References