Novel method for synthesis of some biologically active aminocoumarins

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Nitration of coumarin 4-methyl acetates using concentrated HNO₃ in solvents like chloroform or dichloromethane at lower temperature ‘Cheparon effect’ was found to occur only on aromatic part of coumarin. Yields of nitrocoumarins are almost quantitative and isomers were separated using column chromatographic technique. Reduction of the nitrocoumarins was carried out in environmentally friendly hydride transfer system using Pd/C as catalyst and formic acid or phosphorous acid as hydride generating reagent. Functional groups like -OH, Br, COCH₃, -CH₂COOH and lactone were not interfering in the reduction of nitro group to amino.

In continuation of our work on substituted coumarins (part-I), we reported here synthesis of a few more of this type of coumarins.

Experimental

Melting points are uncorrected. ¹H NMR spectra were recorded on a Bruker spectrometer with TMS as internal reference. The IR spectra were recorded on JASCO-FTIR spectrometer with KBr pellets.

Various coumarins required for the study were prepared using the Pechmann condensation. Coumarin-4-acetic acids were esterified using methanol and catalytic H₂SO₄. Other methyl coumarins were prepared by condensation of substituted phenols with acetoacetic ester. 7-Allyloxy-4-methyl coumarin was prepared by reaction of 7-hydroxy-4-methyl coumarin with allyl bromide. Claissen rearrangement of the allyloxy coumarin yielded 7-hydroxy-4-methyl-8-allyl coumarin. Similarly acetylation of 7-hydroxy-4-methyl coumarins yielded 7-acetoxy 4-methyl coumarin, which on Fries rearrangement gave 7-hydroxy-8-acetyl coumarin.

Methods of preparation of nitro derivatives:

(a) Nitration using HNO₃/CH₂Cl₂:

Nitro dimethyl coumarin-4-methyl acetate: The pre-cooled solution of concentrated HNO₃ (98%) (0.85 ml, 21 mmol) in 40 ml CH₂Cl₂ was added to the solution of dimethyl coumarin-4-methyl acetate (10e-i) (5g, 20 mmol) in CH₂Cl₂ (100 ml) at 5° over a period of one hour. Reaction mixture was stirred at 5° for 1-2 h. Reaction was monitored by TLC till the starting ester completely consumed. Reaction mass was then added to mixture of ice and water and stirred for 30 min. The organic layer was separated and washed with water. The organic layer was then dehydrated and solvent was removed completely under reduced pressure.

In case of 5,7-dimethyl and 6,7-dimethyl coumarins, two isomers were seen in the product and were purified by crystallization from ethyl acetate to get one pure isomer. Other isomer was separated by column chromatography on silica column using toluene : ethyl acetate (90 : 10) mixture as an eluent.

In case of 6,8-dimethyl coumarin 4-methyl acetate, the crude product was containing around 95% single isomer and was purified by crystallization from ethyl acetate. 11e yield 30%, m.p.158–159°; ¹H NMR (CDCl₃) δH 7.46 (1H, s, C₃H), 6.42 (1H, s, C₃H), 3.81 (2H, s, CH₂), 3.77 (3H, s, CH₃), 2.42 (3H, s, CH₃), 2.19 (3H, s, CH₃); v-max 1732 (CO of lactone), 1625 (CO of ester), 1539, 1342 (NO₂), 2958 (CH₃ stretching); 11f yield 70%, m.p. 134–135°; ¹H NMR (CDCl₃) δH 7.31 (1H, s, C₃H), 6.34 (1H, s, C₃H), 3.62 (2H, s, CH₂), 3.75 (3H, s, CH₃), 2.42 (3H, s, CH₃), 2.16 (3H, s, C₃H); v-max 1748 (CO of lactone), 1725 (CO of ester), 1532, 1344 (NO₂), 3041–2849 (CH₃ stretching); 11g yield 75%, m.p. 164–166°; ¹H NMR (CDCl₃) δH 7.17 (1H, s, C₃H), 6.35 (1H, s, C₃H), 3.95 (2H, s, CH₂), 3.77 (3H, s, CH₃), 2.47 (3H, s, CH₃), 2.35 (3H, s, CH₃); v-max 1725 (CO of lactone), 1705 (CO of ester), 1529, 1342 (NO₂), 3056–2959 (CH₃ stretching); 11h yield 25%, m.p. 140–142°; ¹H NMR (CDCl₃) δH 6.98 (1H, s, C₃H), 6.29 (1H, s, C₃H), 3.95 (2H, s, CH₂), 3.76 (3H, s, CH₃), 2.63 (3H, s, CH₃), 2.35 (3H, s, CH₃); v-max 1741 (CO of lactone), 1729 (CO of ester), 1537, 1341 (NO₂), 3052–2844 (CH₃ stretching); 11i
The mass was drowned in ice and stirred for 2844 (CH₃ stretching).

(lH, s, C₈H), 2.53 (3H, s, CH₃); v_max 1634-1549 (NO₂), 1734 (CO of lactone), 1734 (CO of ester), 1525, 1340 (NO₂), 3070-2844 (CH₃ stretching).

(b) Nitrations using mixed acid (HNO₃/H₂SO₄) :

Nitrations of hydroxycoumarins: Hydroxycoumarins (57 mmol) were dissolved in conc. H₂SO₄ (35 ml) and cooled to 0-5°. A mixture of 70% HNO₃ (57 mmol) and conc. H₂SO₄ (10 ml) was added to it at 0-5° over 2 h. Reaction mixture was stirred at 0-5° for 2 h and then slowly raised to 25-30°. Reaction mass was stirred at 30° for 30-45 min. The mass was drowned in ice and stirred for 30 min and the precipitated solids were isolated by filtration and washed with water and dried.

In case of 7-hydroxy-4-methyl coumarin, the crude product of nitration was purified by crystallization from glacial acetic acid and methyl ethyl ketone to give 6-nitro derivative.

In case of 6-hydroxy-4-methyl coumarin, 2m/m HNO₃ was used to obtain 5,7-dinitro coumarin as major product. In case of 7-hydroxy-4-methyl-3-bromo coumarin, the crude product was purified by column chromatography on silica column first using toluene : pet. ether (50 : 50) to isolate 6-nitro derivative and then using methanol to isolate 8-nitro derivative. Yields, melting points and spectral analysis of the nitro derivatives are as follows.

11e yield 79%, m.p. 213-214°; ¹H NMR (DMSO) δH 7.33 (1H, s, C₆H), 6.41 (1H, s, C₃H), 3.76 (3H, s, CH₃), 3.65 (2H, s, CH₂), 2.48 (3H, s, CH₃), 2.27 (3H, s, CH₃); v_max 1575-1551 (NO₂), 1720 (CO of lactone), 3112-2925 (CH₃ stretching), 3316 (OH); 11b yield 82%, m.p. 249-251°; ¹H NMR (DMSO) δH 10.4 (1H, bs, OH), 8.23 (1H, s, CSH), 6.57 (1H, s, CSH), 2.42 (3H, s, CH₃); v_max 1631 (NO₂), 1730 (CO of lactone), 3067-2925 (CH₃ stretching), 3258 (OH); 11k yield 75%, m.p. 246-248°; ¹H NMR (DMSO) δH 8.26 (1H, bs, OH), 7.2-7.6 (2H, dd, CSH + C6H), 2.6 (3H, s, CH₃); v_max 1631 (NO₂), 1730 (CO of lactone), 3067-2925 (CH₃ stretching), 3258 (OH); 11n yield 24%, m.p. 235-236°; ¹H NMR (DMSO) δH 8.54 (2H, bs, OH + C5H), 8.36 (1H, s, C5H), 2.53 (3H, s, CH₃); v_max 1634-1549 (NO₂), 1752 (CO of lactone), 3084 (CH₃ stretching), 3182 (OH).

c) Nitrations using HNO₃/acetic acid :

Nitrations of simple coumarin: To 20 g (0.14 mol) coumarin dissolved in 24 ml glacial acetic acid was added a mixture of 11.5 ml nitric acid (sp. gr. 1.5) in 8 ml glacial acetic acid. No appreciable rise of temperature was observed. 7 ml concentrated sulfuric acid was then added to the mixture, when a vigorous reaction started. The reaction mixture was cooled at first and finally heated for a short time on a water bath. A portion of 6-nitrocoumarin which crystallized out, was filtered off. The remaining 6-nitrocoumarin was precipitated by pouring the acid mother liquor into water. The precipitate was collected and washed thoroughly with water. The solids were dissolved in 20% sodium hydroxide solution to give a red colored solution. It was then cooled to room temperature. A very dilute solution of hydrochloric acid was then added until the solution was slightly acidic. The bulky yellow precipitate that formed was allowed to stand for fifteen minutes and then filtered. The product was washed with dilute sodium bicarbonate solution followed by water till free of alkali and dried. It was crystallized from methanol when pale yellowish crystals of 6-nitrocoumarin were obtained.

When the nitration was carried out using mix acid i.e., without using any acetic acid both the isomers were obtained. 6-Nitrocoumarin was isolated by crystallization from methanol and the 8-nitro isomer was isolated from mother liquor by column chromatography after concentration.

Nitrations of 8-acetyl coumarin: 7-Hydroxy-4-methyl-8-acetyl coumarin (20 g, 0.091 mol) was dissolved in glacial acetic acid (40 ml). A solution of 70% HNO₃ (100 ml) in glacial acetic acid (100 ml) was added to it at 0-4° over 2 h. Reaction mixture was stirred for 4-6 h at 0-5° when fine precipitate appeared. Reaction mixture was kept at 4-6° for 24 h. The precipitated solids were isolated by filtration at 5° and washed with acetic acid followed by water and dried to obtain 3-nitro derivative.

Nitrations of 8-allyl coumarin: 7-Hydroxy-4-methyl-8-allyl coumarin (21.7 g, 0.1 mol) was dissolved in 25 ml glacial acetic acid. A solution of 70% HNO₃ (15 ml) in glacial acetic acid (25 ml) was added to it at 0-4° over 2 h. Reaction mixture was stirred for 10-12 h at 0-5°. The reaction was monitored on TLC. On completion, the reaction mixture was poured into ice water and stirred for 1 h. Precipitated solids were filtered and washed well with water and dried to obtain crude product containing mixture of 3-nitro and 6,3-dinitro derivatives. The nitro derivatives thus obtained were separated by column chromatography on silica column using dichloroethane as an eluent, to isolate 6-nitro and 6,3-dinitro derivatives.

Yields, melting points and spectral analysis of the nitro derivatives are as follows.

11c yield 27%, m.p. 193-196°; ¹H NMR (DMSO) δH 7.4-8.43 (4H, m, C₄H + CSH + C6H + C7H), 6.5-6.6 (1H, d, C3H), 7.08-7.12 (1H, d, C₆H), 2.92 (3H, s, CH₃), 2.59 (3H, s, CH₃); v_max 1586-1529 (NO₂), 1746 (CO of lactone), 2936-2380.
Scheme I

(CH<sub>3</sub> stretching), 3085 (OH); **11** yield 85%, m.p. 182–184°; ¹H NMR (DMSO) δ<sub>H</sub> 8.40–8.46 (2H, m, C₄H + C₅H), 7.82–7.85 (1H, s, C₆H), 7.46–7.50 (1H, d, C₈H), 6.58–6.62 (1H, d, C₃H); v<sub>max</sub> 1620 (N₂), 1746 (CO of lactone); ¹¹m yield 50%, m.p. 205–207°; ¹H NMR (DMSO) δ<sub>H</sub> 6.40–6.45 (1H, d, C₃H), 7.44 (1H, s, C₈H), 7.82–7.87 (1H, d, C₄H); **11j** yield 76%, m.p. 142–144°; ¹H NMR (CDCl₃) δ<sub>H</sub> 11.2 (1H, s, OH), 8.31 (1H, s, C₅H), 6.27 (2H, s, C₃H), 5.96–5.88 (1H, m, CH), 5.03–5.18 (2H, m, CH₂), 3.64 (2H, m, CH₂), 2.45 (3H, s, CH₃), 1.33 (3H, s, CH₃); v<sub>max</sub> 1612–1536 (NO₂), 1750 (CO of lactone), 3107–2936 (CH₃ stretching), 3289 (OH); **11j** yield 24%, m.p. 120–122°; **11e** Isolated
by column chromatography of mother liquor after isolation of 6-nitro coumarin from reaction mixture. Similarly 11j* and 11j** were separated by using column chromatography using dichloro ethane as eluent.

Reduction of nitro coumarin:

Reduction using Pd/formic acid: Nitrocoumarins (11a-j) (10 mmol) was dissolved in a mixture of 85% HCOOH (50 ml), t-butanol (25 ml) and ethanol (25 ml). The solution was warmed to 40–50°. 5% Pd/C (2.7 g) was now added to it. Reaction mixture was now refluxed for 2 h. Reaction progress was monitored by TLC. When reaction was complete the mixture was filtered on sintered glass funnel in hot and catalyst cake was washed with hot acetic acid and then with hot ethanol. Product was now isolated either by crystallization from mother liquor and washes or by complete removal of solvent under reduced pressure. Yields, melting points and spectral analysis of all the aminocoumarins prepared are as follows. 12a yield 70%, m.p. 335–338°; 1H NMR (DMSO) δH 9.53 (1H, bs, CH3), 6.83 (1H, d, C8H), 4.67 (1H, s, C3H), 5.89 (2H, s, NH2), 5.63 (2H, bs, NH2), 2.25 (3H, s, CH2); νmax 1664 (CO of lactone), 2985–2927 (CH3 stretching), 3461–3365 (NH2); 12c yield 82%, m.p. 145–147°; 1H NMR (DMSO) δH 7.61–7.66 (1H, d, C7H), 6.89 (3H, m, C8H), 2.6 (3H, s, CH3); νmax 1703 (CO of lactone), 7.32–7.37 (1H, d, C4H), 6.43–6.48 (1H, s, C3H); νmax 1753 (CO of lactone), 3461–3353 (NH2); 12d yield 90%, m.p. 225–227°; 1H NMR (acetone) δH 7.52 (1H, d, C6H), 6.89 (1H, d, C5H), 5.11 (2H, bs, NH2), 2.59 (3H, s, CH3), 2.15 (3H, s, CH3); νmax 1703 (CO of lactone), 1631 (COCH3), 2931 (CH3 stretching), 3222 (OH), 3466–3359 (NH2); 12e yield 75%, m.p. 185–187°; 1H NMR (DMSO) δH 6.73 (1H, s, C5H), 6.38 (1H, s, C3H), 5.09 (2H, bs, NH2), 3.94 (2H, s, CH2), 3.65 (3H, s, CH3), 2.33 (3H, s, CH3), 2.12 (3H, s, CH3); νmax 3434–3365 (NH2), 1736 (CO of lactone), 1710 (CO of ester), 3057–2924 (CH3 stretching); 12f yield 79%, m.p. 235–236°; 1H NMR (DMSO) δH 6.79 (1H, s, C8H), 6.33 (1H, s, C3H), 3.77–3.79 (7H, bs, NH2 + CH2 + CH3), 2.20 (3H, s, CH3), 2.35 (3H, s, CH3); νmax 3186 (NH2), 1754 (CO of lactone), 1652 (CO of ester), 3057–2924 (CH3 stretching); 12g yield 61%, m.p. 213–214°;

Reduction using Pd/phosphorous acid:

Nitro bromo coumarin (11k,m,n) (2.91 g, 10 mol) was dissolved in a mixture of 50% phosphorous acid (10 ml), t-butanol (25 ml) and EtOH (25 ml). The solution was warmed to 40–50°. 5% Pd/C (0.75 mol) was now added to it. Reaction mixture was now refluxed for 2 h. Reaction progress was monitored by TLC. When reaction was complete reaction mixture was filtered on sintered glass funnel in hot and catalyst cake was washed with hot acetic acid and then with hot ethanol. Product was now isolated by complete concentration under reduced pressure followed by treatment with water to get rid of phosphorous acid. Yields, melting points and spectral data of bromo amino coumarins are as follows. 12k yield 74%, m.p. 255–258° (decomposition); 1H NMR (DMSO) δH 8.26 (1H, bs, OH), 7.2–7.6 (2H, dd, C5H + C6H), 2.6 (3H, s, CH3); 12m yield 90%, m.p. 197–198°; 1H NMR (CDCl3) δH 7.96–8.01 (1H, d, C4H), 7.50 (1H, s, C8H), 6.47–6.52 (1H, d, C3H), 4.64 (2H, bs, NH2); νmax 3413–3322 (NH2), 1742 (CO of lactone); 12n yield 77%, m.p. 248–250° (decomposition); 1H NMR (DMSO) δH 8.27 (1H, s, C5H), 7.32 (2H, m, NH2 + C8H + OH), 2.49 (3H, s, CH3); νmax 3145 (NH2), 2902 (OH), 2565 (CH3), 1696 (CO). All the nitro and amino coumarins supported with spectral data, have satisfactory C, H, N analysis data.