

Claisen Rearrangement of 2'-Hydroxy-4-Methyl-4'-Prenyloxychalcone

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Abstract. Claisen rearrangement of 2'-hydroxy-4-methyl-4'-prenyloxychalcone (**2**) using acetic anhydride in dimethylaniline yields four major compounds viz. 2'-hydroxy-4-methyl-4'', 4'', 5''-trimethyldihydrofurano (2'', 3'': 4', 3')chalcone (**3**), 2',4'-diacetoxy-4-methyl-3'-(α, α -dimethylallyl)chalcone (**4**), 2',4'-diacetoxy-4-methyl-5'-(α, α -dimethylallyl)chalcone (**5**), 2',4'-diacetoxy-4-methylchalcone (**6**) and several other minor compounds. All the isolated products were identified on the basis of IR, UV, ¹H-NMR, Mass and Elemental analysis.

Keywords: chalcone, claisen rearrangement, chalcone derivatives

Recently, Hossain *et al.* (Hossain *et al.*, 1996, 1994a, 1994b, 1993a, 1993b) carried out the Claisen rearrangement of chalcones, flavones and other related compounds. We describe herein our another abnormal Claisen rearrangement results of 2'-hydroxy-4-methyl-4'-prenyloxychalcone (**2**) with Ac₂O in dimethylaniline and mild hydrolysis of one of the isolated product (**4**) (scheme-1). The chalcone (**2**) was obtained by the condensation of 2-hydroxy-4-prenyloxyacetophenone (**1**) (Hossain *et al.*, 1993b) with tolualdehyde under alkaline conditions. The isolation of the major products separated by chromatographic technique and their characterization by spectroscopic techniques are reported.

Melting point was determined on an electrothermal melting point apparatus (Gallenkamp) and is uncorrected. IR spectra were recorded (KBr discs) on a FT-IR spectrophotometer, validation (ν_{\max} in cm⁻¹), ¹H-NMR spectra in CDCl₃ on a Bruker (400 MHz) spectrophotometer using TMS as internal standard (chemical shifts in ppm) and UV spectra in methanol on an LKB 4053 Ultraspek spectrophotometer (λ_{\max} in nm). TLC was performed using silica GF₂₅₄. Satisfactory elemental analyses were obtained for all the compounds, structures were in according with the UV, IR and ¹H-NMR data.

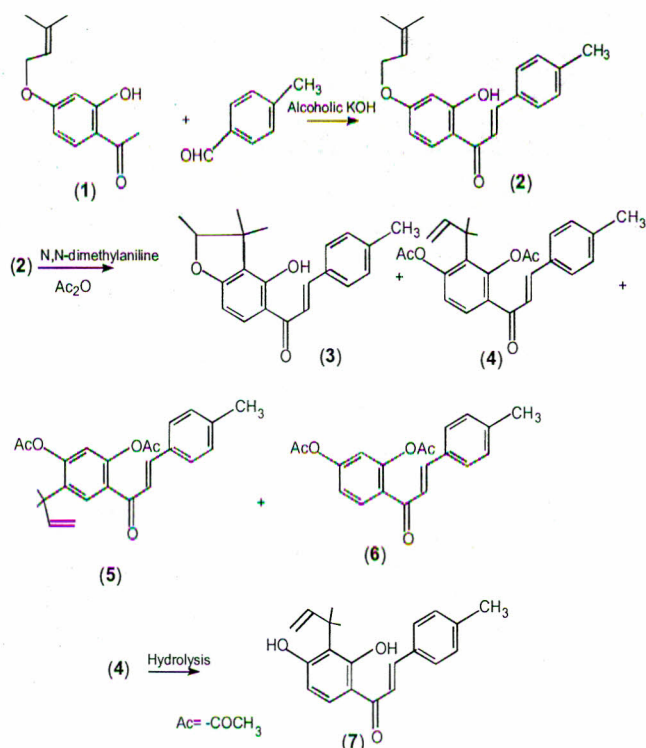
2-Hydroxy-4-prenyloxyacetophenone (1). A solution of β -resacetophenone (15.2 g) in acetone (150 ml) was refluxed with prenylbromide (16.3 g) and anhydrous potassium carbonate (55 g) for 4 h. Acetone was distilled off and water was added to the residue. It was extracted with ether and ether solution was then extracted with 5% aqueous NaOH. The aqueous extract was acidified and extracted with ether. Ether extract on column chromatograph with petroleum spirit gave an oily liquid, which on cooling gave colourless needles

(12 g), yield 54.21%; mp. 47 °C (Hossain *et al.*, 1993b: mp. 46-47 °C); UV: 228, 254, 286 nm; IR: 3555, 1648, 1605, 1595, 1375, 1365 cm⁻¹; ¹H-NMR: δ 1.72 [s, 6H, >C(CH₃)₂], 2.44 (s, 3H, -COCH₃), 4.48 (d, 2H, $J = 7$ Hz, -O-CH₂-CH =), 5.44 (t, 1H, $J = 7$ Hz, -O-CH₂-CH =), 6.73 (dd, 2H, $J = 2.5$ and 9 Hz, H-3 and H-5), 7.55 (d, 1H, $J = 9$ Hz, H-6), 12.76 (s, 1H, -OH); Analysis: found C, 70.89; H, 7.32. C₁₃H₁₆O₃ calc. C, 70.66; H, 7.72%.

2'-hydroxy-4-methyl-4'-prenyloxychalcone (2). A mixture of 2-hydroxy-4-prenyloxyacetophenone (Hossain *et al.*, 1993 b) (**1**, 4.40 g) and tolualdehyde (3.76 g) in 50% ethalonic solution of KOH (50 ml) was kept at room temperature for three days, distilled with ice cold water, acidified with dilute HCl and extracted with ether. The ether layer was washed with water, dried over anhydrous Na₂SO₄ and evaporated to dryness. The products was crystallized from benzene-petroleum spirit (b.p. 40-60 °C) as yellow needles (2.78 g), mp. 78 °C. R_f 0.73 (benzene:acetone; 15:4). It gave brown colour with ferric chloride solution. Mass: m/z 322, M⁺; UV: 230, 245, 375 nm; IR: 3470, 1645, 1600, 1590, 1376, 1363, 998 cm⁻¹; ¹H-NMR: δ 1.75 [s, 6H, >C(CH₃)₂], 2.13 (s, 3H, -CH₃), 4.50 (d, 2H, $J = 7$ Hz, -O-CH₂-CH =), 5.41 (t, 1H, $J = 7$ Hz, -O-CH₂-CH =), 6.45 (dd, 2H, $J = 2.5$ and 9Hz, H-3' and H-5'), 6.84 (d, 2H, $J = 9$ Hz, H-2 and H-6), 6.96 (d, 1H, $J = 9$ Hz, H-6'), 7.18 (d, 1H, $J = 9$ Hz, H-3 and H-5), 7.45 (d, 1H, $J = 15$ Hz, H- α), 8.01 (d, 1H, $J = 15$ Hz, H- β), 12.76 (s, 1H, -OH); Analysis: found C, 78.61; H, 6.60. C₂₁H₂₂O₃ calc. C, 78.30; H, 6.80%.

Claisen rearrangement of 2'-hydroxy-4-methyl-4'-prenyloxychalcone (2). Oxygen free nitrogen was passed for 2 h through a solution of the above chalcone (**2**, 2 g) in immediately distilled N, N-dimethylaniline (20 ml) and acetic anhydride (2 ml) contained in a heavy walled glass tube. The tube was carefully sealed and immersed in an oil bath at 185 \pm 5 °C and kept at this temperature for 4 h. The mixture

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Scheme-1

was diluted with ice-cold water (150 ml), set aside for 2 h and then extracted with ethylacetate. The ethylacetate layer was treated with dilute HCl (1%, w/v) to get pH 2 of the solution followed by aqueous K₂CO₃ (5%, w/v) to pH 11 and finally with brine to neutrality. The organic layer was dried and evaporated to the crude mass. Fractionation of the mass over silica gel column using petroleum spirit, petroleum spirit: ethylacetate (10:5), petroleum spirit: ethylacetate (5:2), petroleum spirit: ethylacetate (5:3), petroleum spirit: ethylacetate (15:2), successively as eluents gave the compounds (3, 4, 5 and 6).

Compound A. Obtained from the column was purified by preparative TLC over silica gel GF₂₅₄ using ethylacetate: *n*-butanol (4:1) as developing solvent and crystallized from xylene as yellow needles (90 mg), yield 5.3%; mp. 46 °C; Mass: m/z 322, M⁺; R_f 0.84 (benzene: *n*-hexane; 15:4); UV: 228, 245, 278, 355 nm; IR: 1765, 1645, 1605, 1593, 1375, 1365 cm⁻¹; ¹H-NMR: δ 1.29 (s, 3H, -CH₃ at C-4"), 1.36 (s, 3H, -CH₃ at C-4"), 1.47 (d, 3H, *J* = 7 Hz, -CH₃ at C-5"), 2.19 (s, 3H, -COCH₃), 4.45 (q, 1H, *J* = 7 Hz, H-5"), 6.73 (d, 2H, *J* = 9 Hz, H-5' and H-6'), 6.98 (d, 2H, *J* = 9 Hz, H-2 and H-6), 7.18 (d, 2H, *J* = 9 Hz H-3 and H-5), 7.48 (d, 1H, *J* = 9 Hz, H-α), 8.01 (d, 1H, *J* = 9 Hz, H-β), 12.75 (s, 1H, -OH); Analysis: found C, 78.55; H, 6.52, C₂₁H₂₂O₃ calc. C, 78.28; H, 6.82%. It was characterised as 2'-hydroxy-4-methyl-4", 4", 5"-trimethyl dihydrofurano (2", 3":4', 3') chalcone (3).

Compound B. It was purified by preparative TLC over silica gel GF₂₅₄ using ethylacetate: *n*-butanol (4:1) as developing solvent, and crystallised from ethylalcohol gave the starting chalcone (2, 180 mg), yield 7%, mp. 78 °C. (Co-UV, Co-IR, Co-NMR and mmp).

Compound C. Obtained from the column was purified by preparative TLC over silica gel GF₂₅₄ using ethylacetate: *n*-butanol (4:1) as developing solvent, and crystallized from dil. alcohol as pale yellow crystals (550 mg), yield 24.58%; mp. 83 °C; Mass: m/z 406, M⁺; R_f 0.71 (benzene: *n*-hexane; 15:4); UV: 225, 244, 365 nm; IR: 1760, 1645, 1605, 1598, 1375, 1365 cm⁻¹; ¹H-NMR: δ 1.45 [s, 6H, >C(CH₃)₂], 2.15 (s, 3H, -CH₃), 2.28 (s, 3H, -COCH₃), 2.41 (s, 3H, -COCH₃), 4.85-4.89 (dd, 2H, *J* = 10 and 18 Hz, H_B and H_C), 6.12-6.18 (dd, 1H, *J* = 10 and 18 Hz, H_A), 6.52-6.58 (dd, 2H, *J* = 2.5 and 9 Hz, H-5' & H-6'), 6.93 (d, 2H, *J* = 9 Hz, H-2 & H-6), 7.15 (d, 2H, *J* = 9 Hz, H-3 and H-5), 7.41 (d, 1H, *J* = 9 Hz, H-α), 8.00 (d, 1H, *J* = 9 Hz, H-β); Analysis: found; C, 73.73; H, 6.64 C₂₅H₂₆O₅ calc. C, 73.92; H, 6.43%. It was characterised as 2', 4'-diacetoxy-4-methyl-3'-(α, α-dimethylallyl) chalcone (4).

Compound D. Isolated fraction from the column was further purified by preparative TLC over silica gel GF₂₅₄ using ethylacetate: *n*-butanol (4:1) as developing solvent, and crystallized from benzene:petroleum spirit as yellow needles (223 mg), yield 37.47%; mp. 65 °C; Mass: m/z 406, M⁺; R_f 0.63 (benzene: *n*-hexane; 15:4); UV: 228, 250, 370 nm; IR: 1755, 1640, 1600, 1595, 1373, 1360 cm⁻¹; ¹H-NMR: δ 1.51 [s, 6H, >C(CH₃)₂], 2.18 (s, 3H, -CH₃), 2.30 (s, 3H, -COCH₃), 2.45 (s, 3H, -COCH₃), 4.81 (dd, 2H, *J* = 10 and 18 Hz, H_B and H_C), 6.23 (dd, 1H, *J* = 10 and 18 Hz, H_A), 6.48 (s, 1H, H-3'), 6.88 (s, 1H, H-6'), 6.99 (d, 2H, *J* = 9 Hz, H-2 and H-6), 7.12 (d, 2H, *J* = 9 Hz, H-3 and H-5), 7.45 (d, 1H, *J* = 9 Hz, H-α), 8.04 (d, 1H, *J* = 9 Hz, H-β); Analysis: found C, 73.65; H, 6.62 C₂₅H₂₆O₅ calc. C, 73.95; H, 6.44%. It was characterised as 2', 4'-diacetoxy-4-methyl-5'-(α, α-dimethylallyl)chalcone (5).

Compound E. Crystallised from water as pale yellow needles (56 mg), yield 15.04%; mp. 49 °C; Mass: m/z 338, M⁺; R_f 0.43 (benzene: *n*-hexane; 15:2); UV: 225, 258, 365 nm; IR: 1760, 1645, 1605, 1378, 1367 cm⁻¹; ¹H-NMR: δ 2.15 (s, 3H, -CH₃), 2.28 (s, 3H, -COCH₃), 2.45 (s, 3H, -COCH₃), 6.49 (dd, 2H, *J* = 2.5 and 9 Hz, H-3' and H-5'), 6.93 (d, 2H, *J* = 9 Hz, H-2 & H-6), 7.01 (d, 1H, *J* = 9 Hz, H-6'), 7.18 (d, 2H, *J* = 9 Hz, H-3 and H-5), 7.49 (d, 1H, *J* = 9 Hz, H-α), 8.02 (d, 1H, *J* = 9 Hz, H-β); Analysis: found C, 71.34; H, 5.52 C₂₀H₁₈O₆ calc. C, 71.95; H, 5.33%. It was characterised as 2', 4'-diacetoxy-4-methylchalcone (6).

Hydrolysis of 4 to 2', 4'-dihydroxy-4-methyl-3'-(α, α-dimethylallyl)chalcone (7). The acetate of (4) (300 mg) was dissolved in ethanol (25 ml) with gentle heating. Sodium

hydroxide in ethanol (1%, w/v, 10 ml) was added to the solution and the mixture was warmed on steam bath for 1 min until the orange-red colour changed to yellow. The solution was then carefully neutralised with cold dilute HCl (1%, w/v) and extracted with ether. The usual work up of the reaction mixture gave a crude product, which on separation by preparative TLC over silica gel GF₂₅₄ using benzene: acetone (15:1) as developing solvent gave the hydrolysis product. The product crystallized from petroleum spirit: benzene as yellow needles (175 mg), yield 52.17%, mp. 91 °C; Mass: m/z 322, M⁺; R_f 0.56 (benzene: acetone; 15:1); It gave yellow colour with alcoholic ferric chloride solution. UV: 225, 255, 380 nm; IR: 3450, 1640, 1600, 1595, 1372, 1360, cm⁻¹; ¹H-NMR: δ 1.45 [s, 6H, >C(CH₃)₂], 2.10 (s, 3H, -CH₃), 4.78-4.83 (dd, 2H, J=10 and 18 Hz, H_B and H_C), 6.21-6.26 (dd, 1H, J=10 and 18 Hz, H_A), 6.65-6.58 (dd, 2H, J=2.5 and 9 Hz, H-5' & H-6'), 6.98 (d, 2H, J=9 Hz, H-2 & H-6), 7.28 (d, 2H, J=9 Hz, H-3 and H-5), 7.45 (d, 1H, J=9 Hz, H-α), 8.10 (d, 1H, J=9 Hz, H-β), 12.5 (s, 1H, -OH); Analysis: found C, 78.54; H, 6.61 C₂₁H₂₂O₃ calc. C, 78.33; H, 6.83%.

The compound (2) was subjected to claisen rearrangement condition and five major compounds (3, 4, 5 and 6) were isolated from the reaction. The compound (3, 4 and 5) are rearranged products in which cases allyl group migrated from the phenolic ring carbons (C-3' and/or C-5'). The preferred formation of 5-membered ring was also supported by ¹H-NMR spectrum. A methyl doublet at δ 1.47 and a methine quartet at δ 4.45 confirmed the formation of a 5-membered ring. The fact that the allyl group has been migrated to C-5 position in this compound was shown by a doublet at δ 6.73 for C-5' and C-6' protons, respectively.

The compound (4) was produced by the migration of allyl group in compound (2) to C-3' of the same aromatic ring followed by oxy-acetylation of the rearranged product at C-4 position. IR and ¹H-NMR spectra have confirmed the observations. IR absorption and frequencies of compound (4), ν 1760 and ν 1645 cm⁻¹ indicated the presence of an ester carbonyl and a conjugated carbonyl group, respectively. ¹H-NMR spectra showed two singlets at δ 2.28 and δ 2.41 indicating the presence of the methyl protons of -COCH₃ group.

The compound (5) is isomeric to compound (4) in which allyl group moiety has migrated to C-5' of the same aromatic ring followed by oxy-acetylation of the rearranged product at C-4'

position. The observation has been confirmed by IR and ¹H-NMR spectra. IR absorption frequencies of compound (5) ν 1755 and 1640 cm⁻¹ indicated the presence of an ester carbonyl and a conjugated carbonyl groups, respectively. ¹H-NMR spectra showed two singlets at δ 2.30 and 2.45 indicating the presence of the methyl protons of -COCH₃ group. Two singlets at δ 6.48 and 6.88 were observed for C-3' and C-6' protons of the aromatic ring.

In compound (6) only oxy-acylation at C-2' of compound (2) has taken place. In IR spectrum a new absorption frequency at ν 1760 cm⁻¹ for ester carbonyl group was observed whereas, the absorption frequency at ν 3470 cm⁻¹ due to phenolic hydroxyl group had disappeared. The compound (7) obtained from compound (4) by its hydrolysis with NaOH in ethanol. IR absorption frequency at ν 1760 cm⁻¹ (ester carbonyl group) was disappeared. In ¹H-NMR spectrum the singlets at δ 2.28 and 2.41 (for CH₃ protons) was disappeared indicating an acyl-oxygen cleavage at C-4', C-2' and C-4 position. The aromatic and other protons have their usual chemical shift values.

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