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Synthesis of Semi-Synthetic Chalcones from the Isolated Intermediate Aldehydes of the Roots of *Decalepis hemiltonii*

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Chalcones, 4-hydroxy-3-(3-(4-methoxy-phenyl)-acryloyl) benzoic acid (a^1), 3-(3-(4-ethoxy-phenyl)-acryloyl)-4-hydroxy-benzoic acid (b^1) were prepared by an aldol condensation between 3-acetyl-4-hydroxy benzoic acid (iv) and isolated aromatic aldehydes from tuberous roots of *Decalepis hemiltonii* in the presence of potassium hydroxide as a base. Flavone, 2-(4-ethoxy-phenyl)-4-oxo-4*H*-chromene-6-carboxylic acid (c^1) prepared from chalcone (b^1) through cyclization *via* bromination. The aromatic aldehydes, anisaldehyde (a), salicylaldehyde (b), vanillin (c), 2-hydroxy-4-methoxy benzaldehyde (d), isovanillin (e), *p*-ethoxy benzaldehyde (f) and benzaldehyde (g) were isolated from the tuberous roots of *Decalepis hemiltonii*. The structures of compounds **i-iv**, **a-g**, **a^1-c^1** were elucidated on the basis of spectral and chemical studies.

Key Words: *Decalepsis hemiltonii,* Chalcone, Flavone, 3-Acetyl-4-hydroxy benzoic acid.

INTRODUCTION

Plant and microorganisms elaborate a diverse range of hererocyclic compounds that are very useful as drugs. The heterocycles are mainly of the classes of chalcones, flavones. Several synthetic compounds of these classes show different bioactivity. More than 50 % of the drugs used in the modern medicine are either synthetic or natural heterocyclic systems.

Natural and synthetic oxygen hereocyclic compounds of the classes of chalcones, flavones, chromenes and chromanones have several useful biological activities[1-4]. The *Decalepsis hamiltoni* (Asclepiadaceae) is an endemic climbing shrub, a native of Peninsular India and distributed in forest areas of the Eastern and Western Ghats, locally known as Nannari in the Telugu language, finds use a culinary spice due to its high-priced aromatic roots rich of aromatic aldehydes[5]. So far no chalcone (a^1), (b^1) and flavone (c^1) synthesis have been carried out on these naturally isolated aldehydes from the roots of *D. hamiltonii*. The present work is the synthesis of flavone intermediates (chalcones) from the isolated aromatic aldehydes from the tuberous roots of *Decalepis hemiltonii* and 3-acetyl-4-hydroxy benzoic acid (iv).

EXPERIMENTAL

The tuberous roots of *Decalepis hamiltoni* (Nannari) were collected from the deciduous forests in Nallamalai forest. For huge extractions, procured from local suppliers in Kurnool, Andhra Pradesh, India.

Extraction and isolation: Freshly harvested roots of *Decalepsis hamiltoni* were washed with tap water and the fleshy portions were separated from the inner woody core manually and cut into small pieces[6] and dried at 40 ºC for 12 h. The dried pieces were ground to powder in a grinder. The dried and coarsely powder (250 g) of tuberous roots was successively extracted with ethanol (10 × 100 mL) in a Soxhlet apparatus[7,8]. The ethanol extract (38 g) on purification over column chromatography (100-200 mesh silica gel) using hexane, ethyl aceatate:hexane and ethyl acetate gradient collected 3 major fractions and fractions purified over silica gel coated glass TLC plate, which afforded 7 compounds, anisaldehyde (a) (60 mg), salicylaldehyde (b) (45 mg), vanillin (c) (40 mg), 2-hydroxy-4-methoxy benzaldehyde (d) (70 mg), isovanillin (e) (50 mg), *p*-ethoxy benzaldehyde (f) (55 mg) and benzaldehyde (g) (25 mg) in minor quantities.

Synthesis of 4-acetoxy benzoic acid methyl ester (iii): To a 4-hydroxy benzoic acid methyl ester (i) (2.5 g; 16.4 mmol) in pyridine (5 mL) was added acetyl chloride (1.54 g; 19.68) drop-wise at 0 ºC. The reaction mixture was stirred for 12 h at ambient temperature. The reaction mixture was concentrated under rota vacuum. The residue was diluted with water, extracted product into ethyl acetate, washed with saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under rota vacuum to afford 4-acetoxy benzoic acid methyl ester (**iii**) (2.4 g; 75 % yield) as a solid.

Synthesis of 3-acetyl-4-hydroxybenzoic acid (iv): A mixture of 4-acetoxy-benzoic acid methyl ester (**iii**) (1 g; 5.15 mmol) and $AlCl_3$ (2.05 g; 15.5 mmol) was heated to 150 ºC, stirred for 5 h. The reaction mixture was cooled to room temperature, quenched with water, extracted product into ethyl acetate and then organic layer was stirred with 5 % $NaHCO_3$ solution, separated bicarbonate layer and then adjusted pH to 5 by using 6 N HCl, washed with water, dried under vacuum to afford 3-acetyl-4-hydroxy benzoic acid (**iv**) (0.6 g; 60 % yield) as a solid.

General procedure for chalcone synthesis: To a solution of aldehyde (1.1 mol) and 3-acetyl-4-hydroxy benzoic acid (**iv**) (1 mol) in ethanol was added 40 % KOH (aq) solution (1.5 mL) slowly dropwise at 0 ºC for 20 min. The reaction was stirred for 48 h at ambient temperature. The reaction mixture was quenched with ice-cold water and adjusted pH to 5 by using 4 N HCl at 20 ºC, stirred for 15 min, filtered solid, washed with water, dried under vacuum, recrystallization in ethanol to afford chalcone as a yellow solid (*ca*. 60 % yield).

Synthesis of 2-(4-ethoxy-phenyl)-4-oxo-4*H*-chromene-6-carboxylic acid (c[1]): Bromine (26 mg; 0.162 mmol) was added to a solution of the chalcone (b[1]) (25 mg; 0.081 mmol) in acetic acid (5 mL) at room temperature. The solution was stirred at ambient temperature for 3 h, 1 % aqueous $NaHSO_3$ (5 mL) was added slowly, the resulting precipitate was filtered, washed with H_2O and suspended in ethanol (5 mL), KOH (18 mg; 0.324 mmol) dissolved in H_2O was added and stirring was confirmed for 4 h. The reaction mixture was acidified by using 2 N HCl to pH = 4 and stirred for 15 min, filtered precipitated solid, then purified through column chromatography (60-120 mesh silica gel), eluted with 8 % methanol/dichloromethane to afford flavone (c[1]) (10.6 mg; 41 % yield) as a yellow solid.

RESULTS AND DISCUSSION

Although some of the aromatic aldehydes isolated form the tuberous roots of *Decalepsis hamiltonii* have been isolated (Fig. 1a-g)[7,9].

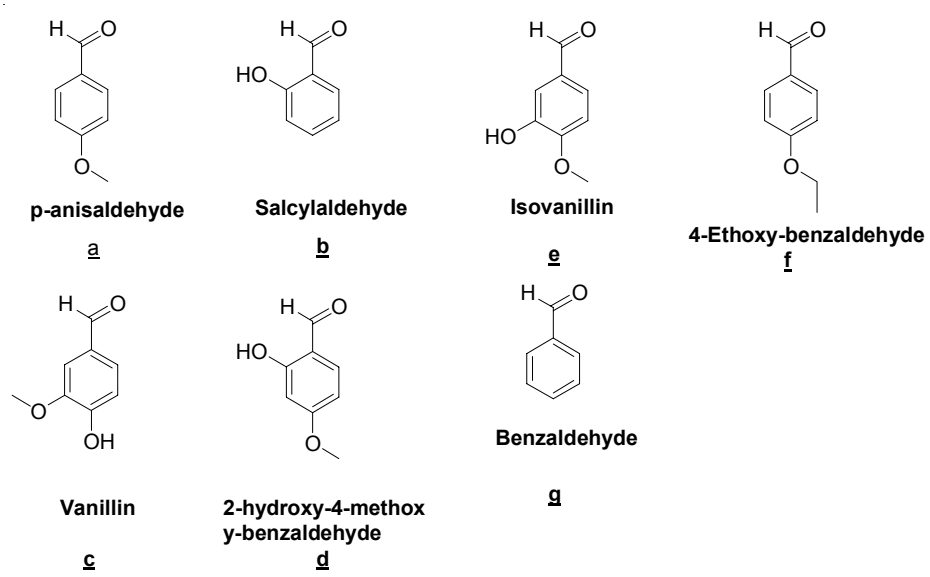


Fig. 1

***p*-Anisaldehyde (a):** ^{1}H NMR 200 MHz ($CDCl_3$): δ 9.84 (s, 1H), 7.81 (d, *J* = 8, 2H), 7.01 (d, *J* = 8, 2H), 3.82 (s, 3H); M^+ (136).

Salcylaldehyde (b): ^{1}H NMR 200 MHz ($CDCl_3$): δ 11.02 (s, 1H), 9.90 (s, 1H), 7.44 (t, *J* = 8.4 Hz, 2H), 7.02 (t, *J* = 8.8 Hz, 2H); M^+ (122).

4-Hydroxy-3-methoxy benzaldehyde (vanillin) (c): ^{1}H NMR 200 MHz ($CDCl_3$): δ 9.81 (s, 1H), 7.41-7.5(m, 2H), 7.01 (d, *J* = 7.9, 2H), 7.01 (d, *J* = 8, 2H), 3.82 (s, 3H); M^+ (152).

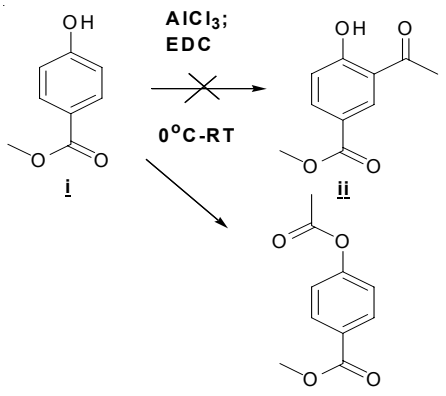
2-Hydroxy-4-methoxy benzaldehyde (d): ^{1}H NMR 200 MHz ($CDCl_3$): δ 11.49 (s, 1H), 9.77 (s, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 6.53 (dd, *J* = 2.4, 2.0 Hz, 1H), 6.43 (d, *J* = 2.2 Hz, 1H), 3.86 (s, 3H); M^+ (152).

3-Hydroxy-4-methoxy benzaldehyde (isovanillin) (e): ^{1}H NMR 200 MHz ($CDCl_3$): δ 9.85 (s, 1H), 7.41-7.45 (m, 2H), 6.97 (d, *J* = 8.8 Hz, 1H), 5.75 (s, 1H), 3.99 (s, 3H); M^+ (152).

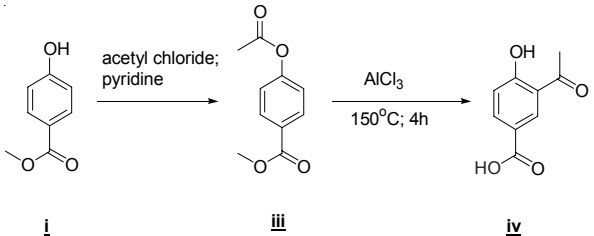
4-Ethoxy benzaldehyde (f): ^{1}H NMR 200 MHz ($CDCl_3$): δ 9.88 (s, 1H), 7.85 (d, *J* = Hz, 2H), 7.01 (d, *J* = Hz, 2H), 4.14 (q, 2H), 1.46 (t, *J* = Hz, 3H); M^+ (150).

Benzaldehyde (g): ^{1}H NMR 200 MHz ($CDCl_3$): δ 10.02 (s, 1H), 7.90 (dd, 2H), 7.44-7.68 (m, 3H); M^+ (106).

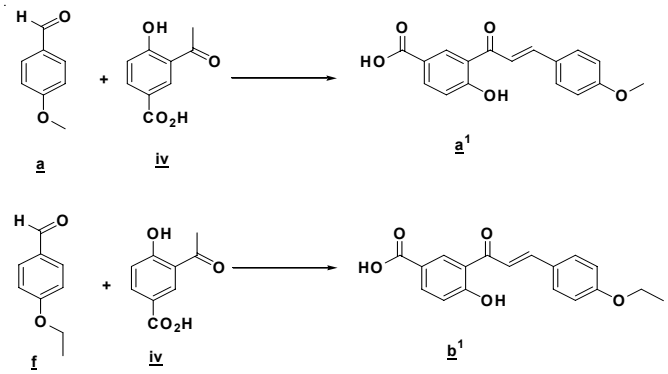
3-Acetyl-4-hydroxy benzoic acid (**iv**) and related chalcones are important for few flavone synthesis. Typically, 3-acetyl-4-hydroxy benzoic acid (**iv**) obtained by acetylation on phenolic OH of 2-hydroxy benzoic acid methyl ester (**i**), followed by fries rearrangement[10], (**Scheme-II**) and related chalcones are obtained by 40 % KOH solution in ethanol at room temperature (**Scheme-III**).



Scheme-I



Scheme-II



Scheme-III

4-Acetoxy benzoic acid methyl ester (**iii**) was resulted instead of expected compound, 3-acetyl-4-hydroxy benzoic acid (**iv**) through **Scheme-I**.

4-Acetoxy-benzoic acid methyl ester (iii): ^{1}H NMR (200 MHz; $CDCl_3$): δ 2.31 (s, 3H), 3.9 (s, 3H), 7.19 (d, 2H), 8.01 (d, 2H): M^+ (195).

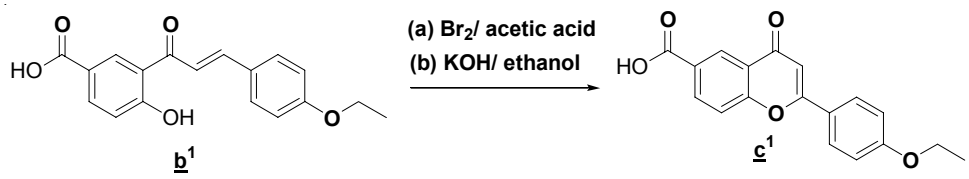
3-Acetyl-4-hydroxy benzoic acid (iv): ^{1}H NMR (200 MHz; DMSO-d_6): δ 2.7 (s, 3H), 7.01(d, 1H), 8.01 (d, 1H), 8.4 (s, 1H), 12.1-12.4 (bs, 1H), 12.7-13.0 (bs, 1H); M^+ (181)

Chalcones were prepared by an aldol condensation between 3-acetyl-4-hydroxy benzoic acid (**iv**) and isolated aromatic aldehydes from tuberous roots of *Decalepis* in the presence of 40 % KOH solution in ethanol at room temperature[11,12].

4-Hydroxy-3-[3-(4-methoxy-phenyl)acryloyl]benzoic acid (a^1): ^{1}H NMR 200 MHz (DMSO-d_6): δ 12.5-12.9 (bs, 1H), 8.55 (s, 1H), 8.03 (d, J = 10.6 MHz, 1H), 7.83 (t, J = 8.8 Hz, 4H), 7.04 (t, J = 8.8 Hz), 3.82 (s, 3H); M^+ (298).

3-[3-(4-Ethoxy-phenyl)acryloyl]-4-hydroxy-benzoic acid (b^1): ^{1}H NMR 200 MHz (DMSO-d_6): δ 12.85 (bs, 1H), 12.77 (bs, 1H), 8.55 (s, 1H), 8.04 (d, J = 10.6 MHz, 1H), 7.83 (t, J = 7.6 Hz, 4H), 6.9-7.08 (m, 3H), 4.10 (q, 2H), 1.33 (t, J = 7 Hz, 3H); M^+ (312)

Flavone (c^1) was prepared by bromination along with cyclization using KOH as base in ethanol at room temperature (**Scheme-IV**)[13,14].



Scheme-IV

2-(4-Ethoxy-phenyl)-4-oxo-4*H*-chromene-6-carboxylic acid (c^1): ^{1}H NMR 200 MHz (DMSO-d_6): δ 8.56 (s, 1H), 8.26 (dd, J = 2.8Hz, 2.7 Hz, 2H), 8.05 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 8.8 Hz, 2H), 6.99 (s, 1H), 4.10 (q, 2H), 1.34 (t, J = 6.6 Hz, 3H); M^+ (310).

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