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COUMARINS *VIA* KNOEVENAGEL CONDENSATION REACTION (KCR) AND PECHMANN CONDENSATION REACTION

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Abstract. Knoevenagel condensation reaction (KCR) and Pechmann condensation reaction are the simplest and most widely used method to synthesize various substituted coumarins. The compounds such as 3-acetylcoumarin, 3-acetyl-7-(diethylamino)coumarin, and 7-(diethylamino)-3-(1-oxobutyl)coumarin were synthesized by KCR method which involved the condensation of salicylaldehyde or 4-(diethylamino)salicylaldehyde with ethyl acetoacetate, 4-(diethylamino)-salicylaldehyde with ethyl butyrylacetate in the presence of dimethylamine as a catalyst. Meanwhile, 7-hydroxy-4-methylcoumarin, 4-methyl-2*H*-benzo[*h*]chromen-2-one, 7-hydroxy-4,8-dimethyl- coumarin, 7-hydroxy-4-propylcoumarin, 4-propyl-*2H*-benzo[*h*]chromen-2-one, 7-hydroxy-8-methyl-4-propylcoumarin and 7,8-dihydroxy-4-propylcoumarin were synthesized through Pechmann condensation reaction by condensation of resorcinol, 1-napthol or 2-methylresorcinol with ethyl acetoacetate, and resorcinol, 1-napthol, 2-methylresorcinol or pyrogallol with ethyl butyrylacetate, respectively in the presence of sulphuric acid as a catalyst. All compounds were characterized by spectroscopic techniques using infrared (IR), proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR).

Keywords: Coumarin derivatives; knoevenagel condensation reaction; pechmann condensation reaction

Abstrak. Kondensasi Knoevenagel dan kondensasi Pechmann adalah kaedah yang paling mudah dan digunakan secara meluas bagi mensintesis pelbagai terbitan kumarin. 3-Asetilkumarin, 3-asetil-7-(dietilamino)kumarin dan 7-(dietilamino)-3-(1-oksobutil)kumarin merupakan sebatian yang telah disintensis melalui tindak balas kondensasi Knoevenagel (KCR) antara salisilaldehid atau 4-(dietilamino)salisilaldehid dengan etil asetoasetat, 4-(dietilamino)salisilaldehid dengan etil butirilasetat dan kehadiran dimetilamina digunakan sebagai pemangkin. Sementara itu, kehadiran asid sulfurik sebagai pemangkin, masing-masing menunjukkan resorsinol, 1-naftol atau 2-metilresorsinol dengan etil asetoasetat, resorsinol, 1-naftol, 2-metilresorsinol atau pyrogallol dengan etil butirilasetat dapat mensintesiskan 7-hidroksi-4-metilkumarin, 4-metil-2*H*- benzo[*h*] -kromen-2-on, 7-hidroksi-4,8-dimetilkumarin, 7-hidroksi-4-propilkumarin, 4-propil-*2H*- benzo[*h*]-kromen-2-on, 7-hidroksi-8-metil-4-propilkumarin dan 7,8-dihidroksi-4-propilkumarin melalui

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tindak balas kondensasi Pechmann. Sebatian yang terhasil kemudiannya dicirikan dengan menggunakan teknik spektroskopi inframerah, resonans magnetik nukleus proton dan karbon (RMN ^{1}H dan ^{13}C).

Kata kunci: Terbitan kumarin; tindak balas kondensasi knoevenagel; tindak balas kondensasi pechmann

1.0 INTRODUCTION

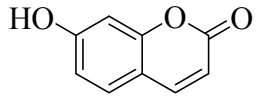
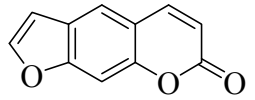
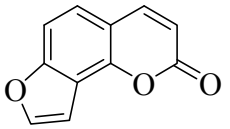
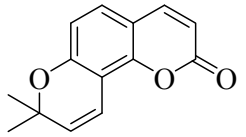
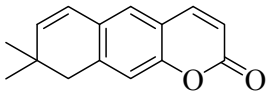
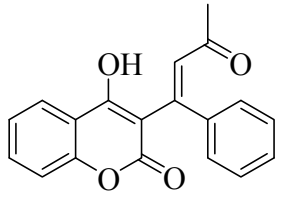
Coumarin (benzopyrones) is a compound containing two structures of six member heterocyclic rings with two oxygen atoms. Classification of coumarins includes simple coumarin, furanocoumarins, pyranocoumarins and coumarins substituted in the pyrone ring (Table 1.1) [1]. Simple coumarins are compound that undergoes hydroxylation, alkoxylation and alkylation to form its derivatives. For furanocoumarins, these compounds consist of five-member furan ring attached to the coumarin nucleus. Pyranocoumarins is a compound that containied a linear or angular type with substituents on benzene and pyrone rings.

Coumarin can be found in several plants notably with high concentration in the tonka bean (*Dipteryx odorata*), vanilla grass (*Anthoxanthum odoratum*), woodruff (*Galium odoratum*), mullein (*Verbascum* spp.), and sweet grass (*Hierochloe odorata*). It has a sweet scent, readily recognised as the scent of newly-mown hay, and has been used in perfumes since 1882. Natural coumarin compounds can be found in flowers, seeds, fruits, trunk, stem and foliage and suitable solvents can be used in extraction for its isolation. Coumarins also can be produced through organic synthesis although it can be found naturally in several green plants. Coumarins and its derivatives can be synthesized through Knoevenagel condensation reaction (KCR), Pechmann condensation reaction, Perkin reaction, Wittig reaction, Claisen, Reformatsky and Kontanecki-Robinson reaction [2].

Coumarins play an important roles as food constituents [3], dye-sensitized solar cells [4] and also used as additives to cigarettes [5]. In addition, coumarins have important effects in plant biochemistry and physiology, acting as antioxidants, enzyme inhibitors and precursors of toxic substances [6]. Coumarin and its derivatives were successfully made great interesting targets for organic chemist due to their chemical properties. The various coumarin derivatives contribute to the expansion of pharmacological, biochemical and therapeutics material. Thus, it is

utmost important to synthesize coumarins and their derivatives through a simple and effective method.

Table 1.1 The four main coumarin subtypes. The main structural features and examples of each coumarin subtype are illustrated in this table

Classification	Features	Examples
Simple coumarins	Hydroxylated, alkoxylated or alkylated on benzene ring	 7-Hydroxycoumarin
Furanocoumarins	5-membered furan ring attached to benzene ring. Linear or angular	 Psoralen  Angelicin
Pyranocoumarins	6-membered pyran ring attached to benzene ring. Linear or angular	 Seselin  Xanthyletin
Pyrone- substituted coumarins	Substitution on pyrone ring, often at 3-C or 4-C positions	 Warfarin

2.0 PROBLEM STATEMENT

There are several methods available for the synthesis of coumarin derivatives. The Knoevenagel condensation reaction (KCR) and Pechmann condensation reaction were chosen to synthesize coumarin derivatives using salicyaldehyde with an active methylene group and substituted phenols with β-ketoester.

Coumarins have a variety of bioactivities including anticoagulant, dermal photosensitizing, anti-inflammatory, and anti-HIV. So, the screening of

bioactivities such as anti-bacterial and anti-platelet for the synthesized coumarin derivatives will be carried out.

3.0 EXPERIMENTAL

3.1 General Instruments and Apparatus

In the synthesis of coumarins, two basic spectroscopic techniques, infrared spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR) were used to characterize the structure of compounds.

The IR spectra were recorded by using FTIR Shimadzu Model 8300 in the range 4000 cm^{-1} to 450 cm^{-1}. Potassium bromide (KBr) disc was used in sample preparation. Meanwhile ^{1}H NMR and ^{13}C NMR spectra were recorded by using Bruker Avance 400 MHz spectrometer with the solvents of aceton-d, $CDCl_3$, or CD_3OD.

Thin layer chromatography (TLC) was used to monitor the progress of reaction, identify the compounds present in a given substance and to determine the purity of a compound. The spot of the compounds can be easily detected by using UV lamp (254nm). TLC was performed on a sheet of aluminium foil, which is coated with a thin layer of silica gel with the thickness of 0.2 mm. The solvent used in TLC were a series of solvents in different polarity.

3.2 Chemical

The chemicals used in this study were salicyaldehyde, 4-(diethylamino)-salicylaldehyde, resorcinol, α-napthol, 2-methylresorcinol, pyrogallol, ethyl acetoacetate, ethyl butyrylacetate, dimethyl amine, concentrated sulphuric acid, dimethyl amine and piperidine. Methanol and absolute ethanol were used as solvent.

3.3 Synthesis of Coumarin Derivatives Through Knoevenagel Condensation Reaction

KCR involves a condensation reaction between an aldehyde or a ketone and a compound containing an active methylene group. The reaction is followed by a dehydration reaction in which a water molecule is eliminated. KCR methods were used to synthesize 3-acetylcoumarin **(1)**, 3-acetyl-7-(diethylamino)-coumarin **(2)** and 7-(diethylamino)-3-(1-oxobutyl)coumarin **(3)**.

3.3.1 3–Acetylcoumarin (1)

2-Hydroxybenzaldehyde (3.0 mL), ethyl acetoacetate (3.1 mL) were placed in 50 mL round bottom flask and 15 drops of dimethyl amine was added. The mixture was stirred and heated for 30 minutes until yellow brown vigorous solution formed. After that, absolute ethanol (18 mL) was added to the reaction mixture and fine precipitate was formed immediately. The product was collected by suction filtration and re-crystallized from ethanol to afford compound **(1)** as a yellow crystalline solid (0.88 g, 18.7%) with melting point 112.5-115°C (lit [7] 119-122°C); R_f 0.47 in hexane: ethyl acetate (4:1). IR: ν_{max} cm^{-1} (KBr); 3030.1 (C-H sp^2), 1741.6 (C=O lactone), 1678.0 (C=O), 1557.3 and 1454.2 (C=C aromatic), 1210.6 (C-O); ^{1}H NMR: δ ($CDCl_3$); 8.32 (1H, s, H-4), 7.63 (2H, m, H-5 and H-8), 7.37 (2H, m, H-6 and H-7), 2.75 (s, -$COCH_3$); ^{13}C NMR: δ ($CDCl_3$); 195.5 (C=O ketone), 159.3 (C=O ester), 155.3 (C-8a), 147.5 (C-4), 134.4 (C-3), 130.2 (C-7), 125.0 (C-5), 124.6 (C-6), 118.3 (C-4a), 116.7 (C-8), 30.6 (CH_3).

3.3.2 3–Acetyl–7–(diethylamino)coumarin (2)

3-Acetyl-7-(diethylamino)coumarin **(2)** was synthesized through KCR method which involved the condensation of 4-(diethylamino)salicylaldehyde with ethyl acetoacetate and piperidine as a base. The preparation of compound **(2)** is in accordance with the preparation of compound **(1)**. Compound **(2)** was formed as a yellow crystalline solid (0.21 g, 38.9%) with melting point 149.5-152.5°C; R_f 0.28 in hexane: ethyl acetate (3:1). IR: ν_{max} cm^{-1} (KBr); 3116.3 (C-H sp^2), 2966.4 (C-H

sp^3), 1723.6 (C=O lactone), 1661.6 (C=O ketone), 1568.6 and 1473.1 (C=C aromatic), 1214.8 (C-N), 1186.3 (C-O); ^{1}H NMR: δ ($CDCl_3$); 8.45 (1H, s, H-4), 7.41 (1H, d, *J* = 9.2 Hz, H-5), 6.63 (1H, dd, *J* = 9.2 and 2.4 Hz, H-7), 6.48 (1H, d, *J* = 2 Hz, H-8), 3.47 (4H, q, *J* = 6.8 and 7.2 Hz, CH_2-7a and CH_2-7b), 2.69 (3H, s, CH_3), and 1.25 (6H, t, *J* = 7.2 Hz, CH_3-7c and CH_3-7d); ^{13}C NMR: δ ($CDCl_3$); 12.4 (CH_3-7c and CH_3-7d), 30.6 (CH_3 for C-3), 45.1 (CH_2-7a and CH_2-7b), 96.6 (C-8), 108.2 (C-4a), 109.8 (C-6), 116.2 (C-3), 131.9 (C-5), 147.8 (C-4), 153.0 (C-7), 158.8 (C-8a), 160.9 (C=O lactone), and 195.7 (C=O ketone).

3.3.3 7–(Diethylamino)–3– (1–oxobutyl)coumarin (3)

7-(Diethylamino)-3-(1-oxobutyl)coumarin **(3)** was synthesized through KCR method which involved the condensation of 4-(diethylamino)salicylaldehyde with ethyl butyrylacetate and piperidine as a base. The preparation of compound **(3)** is in accordance with the preparation of compound **(1)**. The crystalline solid was re-crystallized from ethanol to give compound (3) as a yellow needles (0.12 g, 20.3%) with melting point 125.5-128°C; R_f 0.39 in hexane: ethyl acetate (3:1). IR: ν_{max} cm^{-1} (KBr); 3108.8 (C-H *sp*^{2}), 2969.5 (C-H *sp*^{3}), 1719.3 (C=O lactone), 1610.6 (C=O ketone), 1568.3 and 1492.4 (C=C aromatic), 1255.4 (C-N), 1174.1 (C-O); ^{1}H NMR: δ ($CDCl_3$);8.44 (1H, s, H-4), 7.41 (1H, d, *J* = 8.8 Hz, H-5), 6.62 (1H, dd, *J* = 8.8 Hz and 2.4 Hz, H-6), 6.48 (1H, d, *J* = 2.4 Hz, H-8), 3.46 (4H, q, *J* = 6.8 Hz and 7.2 Hz, CH_2-7a and CH_2-7b), 3.10 (2H, t, *J* = 7.2 Hz, CH_2-3b), 1.72 (2H, m, CH_2-3c), 1.25 (6H, t, *J* = 7.2 Hz, CH_3-7c and CH_3-7d) and 0.99 (3H, t, *J* = 7.2 Hz, CH_3-3d).

3.4 Synthesis Of Coumarin Derivatives Through Pechmann Conensation Reaction

The Pechmann condensation reaction consists in the formation of comarins by aldol condensation of substituted phenols with β-ketoester in the presence of an acid catalyst. Pechmann condensation reaction was used to synthesize 7-hydroxy-4-methylcoumarin **(4)**, 4-methyl-2*H*–benzo [*h*]chromen-2-one **(5)**, 7-hydroxy-4,8-dimethylcoumarin **(6)**, 7-hydroxy-4-propylcoumarin **(7)**, 4-propyl-*2H*-

benzo[*h*]chromen-2-one **(8)**, 7-hydroxy-8-methyl-4-propyl- coumarin **(9)**, and 7,8-dihydroxy-4-propylcoumarin **(10)**.

3.4.1 7–Hydroxy–4–methylcoumarin (4)

Resorcinol (6.61 g, 0.06 mole), ethyl acetoacetate (7.6 mL, 0.06 mole) were placed in an Erlemenyer flask (50 ml) and concentrated sulphuric acid, H_2SO_4 (75%, 30 mL) was added. The mixture was placed on the stirrer/ heater then stirred at 94°C for an hour. The mixture was poured into crushed ice with the constant stirring until the precipitate was formed. Then the reaction mixture was neutralized to litmus to get solid product and collected by using suction filtration. The solid product washed with water, dried and re-crystallized from methanol to give 7-hydroxy-4-methylcoumarin **(4)** as a pale yellow solid (6.24 g, 59.0%) with melting point 182-184.5°C (lit [8] 185-187°C); R_f 0.42 in hexane : ethyl acetate (3:2). ^{1}H NMR: δ (CD_3COCD_3); 7.63 (1H,d, *J* = 8.8 Hz, H-5), 6.87 (1H, dd, *J* = 8.8 Hz and 2.4 Hz , H-6), 6.75 (1H, d, *J* = 2.4 Hz, H-8), 6.09 (1H, s, H-3), 2.43 (3H, s, CH_3); ^{13}C NMR: δ (CD_3COCD_3); 22.8 (CH_3), 107.5 (C-8), 116.1 (C-3), 117.7 (C-6), 117.9 (C-4a), 131.6 (C-5), 158.1 (C-8a), 160.7 (C-4), 165.4 (C-7), and 166.1 (C=O).

3.4.2 4–Methyl–2H–benzo[h]chromen–2–one (5)

4-Methyl-*2H*-benzo[*h*]chromen-2-one **(5)** was synthesized by Pechmann condensation reaction method which involved the condensation of α-napthol with ethyl acetoacetate and sulphuric acid as a catalyst. The preparation of compound **(5)** is in accordance with the preparation of compound **(4)**. Compound **(5)** was formed as a grey crytalline solid (0.92 g, 14.1%) with melting point 167-169°C (lit [9] 168°C); R_f 0.72 in hexane: ethyl acetate (3:2). IR: ν_{max} cm^{-1} (KBr); 3071.8 (C-H *sp*^{2}), 2918.1 (C-H *sp*^{3}), 1715.9 (C=O lactone), 1610.3 and 1473.1 (C=C aromatic), 1083.9 (C-O); ^{1}H NMR: δ ($CDCl_3$); 8.58 (1H, m, H-10), 7.88 (1H, m, H-7), 7.71 (1H, d, *J* = 8.8 Hz, H-5), 7.65 (2H, m, H-8 and H-9), 7.61 (1H, d, *J* = 8.8 Hz, H-6), 6.39 (1H, s, H-3), 2.54 (s, CH_3); ^{13}C NMR: δ ($CDCl_3$); 19.2 (CH_3), 114.4 (C-3), 115.2 (C-6), 120.3 (C-10), 122.7 (C-5), 123.2 (C-4a), 124.1 (C-10a), 127.1 (C-8),

127.6 (C-9), 128.6 (C-7), 134.8 (C-6a), 150.7 (C-4), 153.4 (C-10b), and 160.9 (C=O).

3.4.3 7– Hydroxy–4,8–dimethylcoumarin (6)

7-Hydroxy-4,8-dimethylcoumarin **(6)** was synthesized by Pechmann condensation reaction method which involved the condensation of 2-methylresorcinol with ethyl acetoacetate and concentrated sulphuric acid as a catalyst. The preparation of compound **(6)** is in accordance with the preparation of compound **(4)**. Compound **(6)** formed as a white solid (3.56 g, 31.2%) with melting point 258-260.5°C (lit [10] 257-258°C); R_f 0.43 in hexane: ethyl acetate (3:2). IR: ν_{max} cm^{-1} (KBr); 3218.2 (O-H), 3005.5 (C-H sp^2), 2921.6 (C-H sp^3), 1686.1 (C=O lactone), 1605.9 (C=C aromatic), 1089.6 (C-O); ^{1}H NMR: δ (CH_3OD); 7.46 (1H, d, *J* = 8.4 Hz, H-5), 6.85 (1H, d, *J* = 8.8 Hz, H-6), 6.10 (1H, s, H-3), 2.43 (3H, s, CH_3 for C-8) and 2.25 (3H, s, CH_3 for C-4); ^{13}C NMR: δ (CH_3OD); 6.7 (CH_3 for C-8), 17.3 (CH_3 for C-4), 109.4 (C-3), 111.5 (C-6), 111.7 (C-4a), 112.5 (C-8), 122.7 (C-5), 153.0 (C-8a), 155.1 (C-4), 159.3 (C-7), 162.9 (C=O).

3.4.4 7–Hydroxy–4–propylcoumarin (7)

The reaction between resorcinol with ethyl butyrylacetate and concentrated sulphuric acid as a catalyst produced 7-hydroxy-4-propylcoumarin **(7)**. The preparation of compound **(7)** is in accordance with the preparation of compound **(4)**. Compound **(7)** formed as a yellow crystalline solid (2.41 g, 38.1%) with melting point 133.5-136°C (lit [11] 135-137°C); R_f 0.46 in hexane: ethyl acetate (3:2). IR: ν_{max} cm^{-1} (KBr); 3199.8 (O-H), 3058.0 (C-H sp^2), 2961.8 (C-H sp^3), 1696.7 (C=O lactone), 1617.6 and 1458.0 (C=C aromatic), 1140.1 (C-O); ^{1}H NMR: δ (CD_3COCD_3); 7.67 (1H, d, *J* = 8.8 Hz, H-5), 6.86 (1H, dd, *J* = 8.8 Hz and 2.4 Hz, H-6), 6.76 (1H, d, *J* = 2.0 Hz, H-8), 6.06 (1H, s, H-3), 2.77 (2H, t, *J* = 7.6 Hz, CH_2-b), 1.72 (2H, m, CH_2-a), and 1.04 (3H, t, *J* = 7.2 Hz, CH_3); ^{13}C NMR: δ (CD_3COCD_3); 13.2 (CH_3), 21.6 (CH_2-b), 33.3 (CH_2-a), 102.6 (C-8), 110.0 (C-3), 112.0 (C-6), 112.6 (C-4a), 126.2 (C-5), 155.8 (C-8a), 156.5 (C-4), 160.3 (C-7) and 160.8 (C=O).

3.4.5 4–Propyl–2H–benzo[h]chromen–2–one (8)

α-Napthol (1.9 g, 0.013 mole), ethyl butyrylacetate (2.0 ml, 0.013 mole) were placed in an Erlemenyer flask (50 ml) and concentrated sulphuric acid, H_2SO_4 (75%, 15 ml) was slowly added. The reaction mixture was stirred at room temperature for overnight. The reaction mixture was poured into crushed ice with the constant stirring until the precipitate was formed. Then the reaction mixture was neutralized to litmus to get solid product and collected by using suction filtration. The solid product washed with water, dried and recrystallized from a minimum amount of methanol (charcoal) to afford 4-propyl-*2H*-benzo[*h*]chromen-2-one **(8)** as a white crystalline solid (in needles) (0.69 g, 22.3%) with melting point 116-117.5°C; R_f 0.84 in hexane: ethyl acetate (3:2). IR: ν_{max} cm^{-1} (KBr); 3047.5 (C-H sp^2), 2960.6 (C-H sp^3), 1722.9 (C=O lactone), 1607.0 and 1471.0 (C=C aromatic), 1071.2 (C-O); ^{1}H NMR: δ ($CDCl_3$); 8.59 (1H, m, H-10), 7.88 (1H, m, H-7), 7.72 (1H, d, J = 8.8 Hz, H-6), 7.65 (3H, m, H-5, H-8, H-9), 6.39 (1H, s, H-3), 2.86 (2H, t, J = 7.6 Hz, CH_2-a), 1.81 (2H, m, CH_2-b) and 1.11 (3H, t, J = 7.6 Hz, CH_3); ^{13}C NMR: δ ($CDCl_3$); 13.9 (CH_3), 21.6 (CH_2-b), 34.3 (CH_2-a), 113.3 (C-3), 114.7 (C-4a), 120.2 (C-6), 122.7 (C-10), 123.4 (C-5), 124.1 (C-10a), 127.1 (C-8), 127.6 (C-9), 128.6 (C-7), 134.7 (C-6a), 150.9 (C-10b), 157.1 (C-4), and 161.1 (C=O).

3.4.6 7–Hydroxy–8–methyl–4–propylcoumarin (9)

7-Hydroxy-8-methyl-4-propylcoumarin **(9)** was prepared by Pechmann condensation reaction which involved the condensation of 2-methylresorcinol with ethyl butyrylacetate and sulphuric acid as a catalyst. The preparation of compound **(9)** is in accordance with the preparation of compound **(8)**. Compound **(9)** was formed as a white solid (0.61 g, 21.5%) with melting point 166-169°C; R_f 0.57 in hexane: ethyl acetate (3:2). IR: ν_{max} cm^{-1} (KBr); 3329.2 (O-H), 3046.9 (C-H sp^2), 2965.1 (C-H sp^3), 1698.4 (C=O lactone), 1602.0 and 1506.6 (C=C aromatic), 1084.8 (C-O); ^{1}H NMR: δ (CD_3COCD_3); 7.51 (1H, d, J = 8.8 Hz, H-5), 6.91 (1H, d, J = 8.8 Hz, H-6), 6.06 (1H, s, H-3), 2.77 (2H, t, J = 7.6 Hz, CH_2-b), 2.25 (3H, s, CH_3 (for C-8)), 1.73 (2H, m, CH_2-a), and 1.04 (3H, t, J = 7.6 Hz, CH_3 (for C-4)); ^{13}C NMR: δ (CD_3COCD_3); 7.3 (CH_3 (for C-8)), 13.2 (CH_3), 21.7 (CH_2-a), 33.4

(CH_2-b), 109.6 (C-3), 111.6 (C-6), 111.9 (C-4c), 122.7 (C-5 and C-8), 153.7 (C-8a), 156.8 (C-4), 158.6 (C-7) and 160.5 (C=O).

3.4.7 7,8–Dihydroxy–4–propylcoumarin (10)

7,8-Dihydroxy-4-propylcoumarin **(10)** was synthesized through Pechmann condensation reaction which involved the condensation of pyrogallol with ethyl butyrylacetate and sulphuric acid as a catalyst. The preparation of compound **(10)** is in accordance with the preparation of compound **(8)**. Compound **(10)** was synthesized as a yellowish solid (0.80 g, 28.0%) with melting point 166-168°C; R_f 0.86 in ethyl acetate: acetone (3:2). IR: ν_{max} cm^{-1} (KBr); 3274.0 (O-H), 3114.5 (C-H sp^2), 2964.3 (C-H sp^3), 1686.0 (C=O lactone), 1581.1 and 1453.3 (C=C aromatic), 1044.7 (C-O); ^{1}H NMR: δ (CD_3COCD_3); 7.22 (1H, d, J = 8.8 Hz, H-5), 6.88 (1H, d, J = 8.8 Hz, H-6), 6.06 (1H, s, H-3), 2.76 (2H, t, J = 7.6 Hz, CH_2-a), 1.73 (2H, m, CH_2-b), and 1.04 (3H, t, J = 7.2 Hz, CH_3)); ^{13}C NMR: δ (CD_3COCD_3); 13.2 (CH_3), 21.8 (CH_2-b), 33.4 (CH_2-a), 109.8 (C-4a), 111.9 (C-5), 112.5 (C-6), 115.6 (C-3), 132.1 (C-4), 143.5 (C-8a), 148.7 (C-7), 157.1 (C-8), and 159.9 (C=O).

4.0 RESULTS AND DISCUSSION

Three coumarin derivatives were synthesized through KCR such as 3-acetylcoumarin **(1)** [7], 3-acetyl-7-(diethylamino)coumarin **(2)** [12] and 7-(diethylamino)-3-(1-oxobutyl)coumarin **(3)**. Meanwhile, 7-hydroxy-4-methyl-coumarin **(4)** [8], 4-methyl-*2H*-benzo[*h*]chromen-2-one **(5)** [9], 7-hydroxy-4,8-dimethylcoumarin **(6)** [10], 7-hydroxy-4-propylcoumarin **(7)** [11], 4-propyl-*2H*-benzo[*h*]chromen-2-one **(8)**, 7-hydroxy-8-methyl-4-propylcoumarin **(9)** and 7,8-dihydroxy-4-propylcoumarin **(10)** were synthesized through Pechmann condensation reaction. The particular compounds including 3-acetyl-7-(diethylamino)coumarin (2) [12], 7-(diethylamino)-3-(1-oxobutyl)coumarin (3), 4-propyl-*2H*-benzo[*h*]chromen-2-one **(8)**, 7-hydroxy-8-methyl-4-propylcoumarin **(9)** and 7,8-dihydroxy-4-propylcoumarin **(10)** had been successfully synthesis previously. But up to now, there is still not been reported for the melting point.

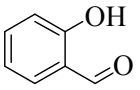
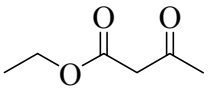
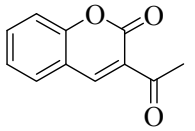
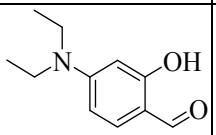
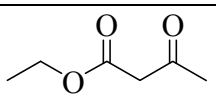
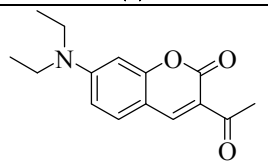
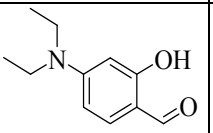
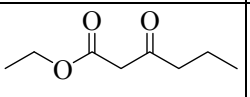
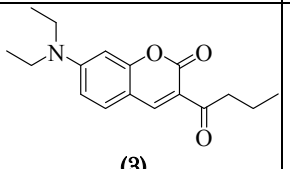
Coumarin derivatives were synthesized by KCR and Pechmann condensation reaction. KCR methods involved the condensation of an aldehyde with a

compound containing an active methylene group. The reaction was carried out in the presence of catalytic amount of base while the Pechmann condensation reaction consists in the formation of coumarin derivatives by aldol condensation of substituted phenols with β-ketoester in the presence of an acid catalyst [13].

All coumarin derivatives which were synthesized through Knoevenagel condensation reaction are summarized in Table 4.1. 3-Acetylcoumarin **(1)** was synthesized by Knoevenagel condensation reaction which involved the condensation of salicyaldehyde with ethyl acetoacetate in the presence of dimethylamine as a base. The reaction was started by the formation of enolate ion which involved the carbonion attacked to the slightly positive carbon on the salicylaldehyde, and the carbonyl oxygen recaptures the original proton which was extracted in the formation of the enolate. The lone pair on the new hydroxyl group removes the hydrogen on the α-carbon. The α-carbon then donates its lone pair to form a double bond, and elimination of water gave 3-acetylcoumarin **(1)**.

Structure of the compounds was confirmed by IR, ^{1}H and ^{13}C NMR and data for these compounds are shown in experimental procedure section. The IR spectrum of compound **(1)** showed absorption bands for C-H sp^2 at 3030.1 cm^{-1}, C=O (1678.0 cm^{-1}) and C=O lactone (1741.6 cm^{-1}). While the two sharp and strong bands of absorption at 1557.3 cm^{-1} and 1458.2cm^{-1} showed the presence of C=C aromatic ring system. The ^{1}H NMR spectrum of compound **(1)** exhibited one singlet signal located at δ 2.75 attributed to the proton for methyl group. Finally the structure was supported by its ^{13}C NMR spectrum which the signals for two carbonyl carbons were observed at δ 159.3 and δ 195.5. Compound **(2)** had one characteristic signal appeared at δ 3.47 for two methylene group (CH_2-7a and CH_2-7b). Therefore, the structure of compound **(2)** was confirmed by its ^{13}C NMR spectrum which C-7 appeared at δ 153.0. The ^{1}H NMR spectrum compound **(3)** showed two doublet signals at δ 6.48 (1H) and δ 7.41 (1H) which were represented to the aromatic proton H-8 and H-5 with the *J* values of 2.4 and 8.8 Hz respectively. The aromatic proton of H-8 was *ortho* coupled with H-7 but aromatic proton H-5 was *meta* coupled with H-7 which were resonated at δ 6.62 as doublet of doublets with *J* values of 8.8 and 2.4 Hz.

Table 4.1 Synthesis of coumarin derivatives from salicyaldehyde and an active methylene group catalyzed by dimethylamine or piperidine

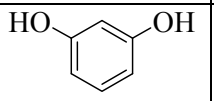
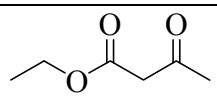
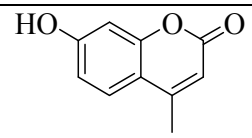
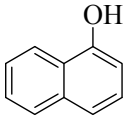
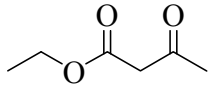
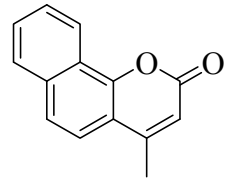
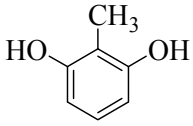
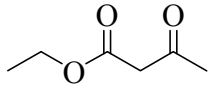
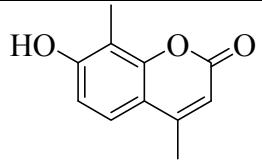
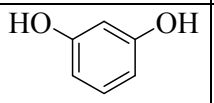
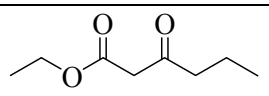
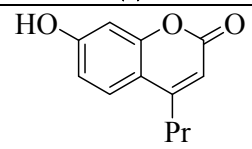
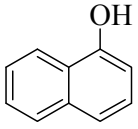
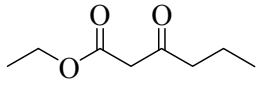
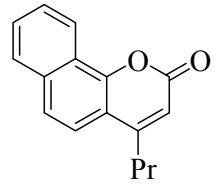
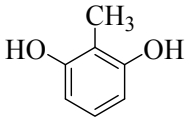
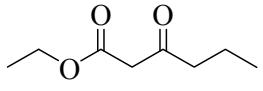
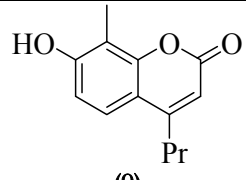
Salicyaldehyde	Active methylene group	Product	Melting point, °C	Yield, %
		 (1)	112.5-115°C (lit [7] 119-122°C)	18.7
		 (2)	149.5-152.5°C	38.9
		 (3)	125.5-128°C	20.3

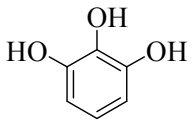
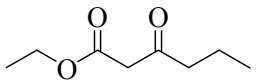
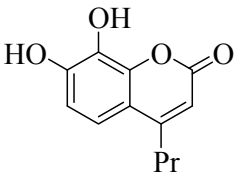
Coumarin derivatives which were synthesized through Pechmann condensation reaction are summarized in Table 4.2. The reaction between resorcinol with ethyl acetoacetate in the presence of sulphuric acid through Pechmann condensation produced 7-hydroxy-4-methylcoumarin **(4)** as a pale yellowish solid in 59.0% yield with melting point 182-184.5°C (lit [7] 185-187°C). The reaction was initiated by the attacked of β-keto carbonyl carbon of the ketoester from the hydroxyl oxygen to form β-ketoester. The keto-enol tautomerisation of the ester and its enol of structure are induced by addition of acid catalyst. A Michael addition leads to the formation of the coumarin skeleton. This addition is followed by rearomatisation. The subsequent acid induced elimination of water gave 7-hydroxy-4-methylcoumarin **(4)**.

The ^{1}H NMR spectrum of compound **(4)** exhibited two doublet signals at δ 6.75 and δ 7.63 which were represented to the aromatic proton H-8 and H-5 with the *J* values of 2.4 and 8.8 Hz. The aromatic proton of H-5 was *ortho* coupled with H-6 but aromatic proton H-8 was *meta* coupled with H-6 which were resonated at δ 6.87 as doublet of doublets with *J* values of 8.8 and 2.4 Hz. Finally the structure

of compound **(4)** was supported by ^{13}C NMR spectrum with two signals at δ 160.7 and δ 165.4were attributed for C-4 and C-7.

Table 4.2 Synthesis of coumarin derivatives from phenols and β-keto esters catalyzed by base

Phenol	**β-Keto Esters**	**Product**	**Melting point, °C**	**Yield, %**
		 **(4)**	182-184.5 (lit [8] 185-187°C)	59.0
		 **(5)**	167-169 (lit [9] 168°C)	14.1
		 **(6)**	258-260 (lit [10] 257-258°C)	31.2
		 **(7)**	133.5-136 (lit [11] 135-137°C)	38.1
		 **(8)**	116-117.5°C	22.3
		 **(9)**	166-169°C	21.5

		 (10)	166-168°C	28.0

The ^{1}H NMR spectrum showed two characteristic of multiplet signals at δ 7.88 (1H) and δ 8.58 (1H) of compound **(5)** which were attributed to the aromatic proton at H-7 and H-10. The structure was confirmed by its ^{13}C NMR spectrum with the presence of signals for 4 quaternary carbons at C-4a, C-10a, C-6a and C-10b resonated at δ 123.2, δ 124.1, δ 134.8 and δ 153.4.

The ^{1}H NMR spectrum of compound **(6)** displayed one singlet signal which was attributed to the olefinic proton, H-3 at δ 6.10 presences in the structure. The structure was supported by its ^{13}C NMR spectrum with the presence of signals for the methyl carbon (CH_3) at C-8 and C-4 was resonated at δ 6.7 and δ 17.3.

The ^{1}H NMR spectrum of compound **(7)** exhibited three signals at δ 1.04 (3H, t, J = 7.2 Hz), δ 1.72 (2H, m), and δ 2.77 (2H, t, J = 7.6 Hz) which were attributed to the CH_3, CH_2-a and CH_2-b, respectively. The ^{13}C NMR spectrum for compound **(7)** showed the addition of three new signals that were observed at δ 13.2, δ 21.6, and δ 33.3 corresponding to the CH_3, CH_2-a and CH_2-b of the propyl group. Compound **(7)** was identified as 7-hydroxy-4-propylcoumarin based on the spectral data evidence.

The ^{1}H NMR spectrum of compound **(8)** exhibited three signals appeared at δ 1.11 (3H, t, J = 7.6 Hz), δ 1.81 (2H, m), and δ 2.86 (2H, t, J = 7.6 Hz) corresponding to the CH_3, CH_2-a and CH_2-b, respectively. The structure was supported by its ^{13}C NMR spectrum with the presence of signals for four quaternary carbons, C-4a, C-6a, C-10a and C-10b were resonated at δ 114.7, δ 134.7, δ 124.1 and δ 150.9, respectively.

The ^{1}H NMR spectrum for compound **(9)** exhibited *ortho* coupling doublets each at δ 7.51 (1H, J = 8.8 Hz) and δ 6.91 (1H, J = 8.8 Hz) which were attributed to the aromatic proton H-5 and H-6. Three signals each at δ 1.04 (3H, t, J = 7.6 Hz), δ 1.73 (2H, m), and δ 2.77 (2H, t, J = 7.6 Hz) were assigned to CH_3, CH_2-a and CH_2-b. The ^{13}C NMR spectrum of compound **(9)** showed two signals for two

quaternary carbons, C-4a and C-8a which were indicated and resonated at δ 111.9 and δ 153.7, respectively.

The ^{1}H NMR spectrum for compound **(10)** indicated the presence of a singlet signal at δ 6.06 (1H, s) which was attributed to the olefinic proton, H-3. Three signals each at δ 1.04 (3H, t, J = 7.2 Hz), δ 1.73 (2H, m), and δ 2.76 (2H, t, J = 7.6 Hz) were assigned to CH_3, CH_2-b and CH_2-a. The presence of this signals confirmed the success of the condensation reaction to form compound **(10)**. The ^{13}C NMR spectrum spectra showed two signals for the C-7, and C-8 were attributed at δ 148.7 and δ 157.1, respectively. C-7 and C-8 were represented that have two hydroxyl group bonded on this two carbons respectively for compound **(10)**. In addition to these, four quaternary carbons were observed at δ 109.8 (C-4a), δ 143.5 (C-8a), δ 132.1 (C-4) and δ 159.9 (C=O).

6.0 SUMMARY AND CONCLUSION

3-Acetylcoumarin **(1)** (18.7%), 3-acetyl-7-(diethylamino)coumarin **(2)** (38.9%) and 7-(diethylamino)-3-(1-oxobutyl)coumarin **(3)** (20.3%) were successfully synthesized by KCR method which involved the condensation of salicylaldehyde or 4-(diethylamino)salicylaldehyde with ethyl acetoacetate, 4-(diethylamino)-salicylaldehyde with ethyl butyrylacetate, dimethylamine and piperidine as a base.

The synthesis of 7-hydroxy-4-methylcoumarin **(4)** (59.0%), 4-methyl-2*H*-benzo[*h*]chromen-2-one **(5)** (14.1%), 7-hydroxy-4,8-dimethyl-coumarin **(6)** (31.2%), 7-hydroxy-4-propylcoumarin **(7)** (38.1%), 4-propyl-*2H*-benzo[*h*]- chromen-2-one **(8)** (22.3%), 7-hydroxy-8-methyl-4-propylcoumarin **(9)** (21.5%), and 7,8-dihydroxy-4-propylcoumarin **(10)** (28.0%) through Pechmann condensation using resorcinol, α-napthol, or 2-methylresorcinol with ethyl acetoacetate, and resorcinol, α-napthol, 2-methylresorcinol, or pyrogallol with ethyl butyrylacetate. The reactions were catalyzed by sulphuric acid.

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