eProceedings Chemistry 3 (2018) 73-82

eISSN 2550-1453 http://eproceedings.chemistry.utm.my/

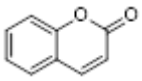
Synthesis and Characterization of 7-Hydroxy-4-Methylcoumarin-3-Ethyl Acetate and Its Derivatives

Joazaizulfazli Jamalis* and Lakshmana Bahrathi Satiyamurti

Department of Chemistry, Faculty of Science, Universiti Teknologi Malaysia, 81310 Johor Bahru, Malaysia
Corresponding Author: joazaizul@kimia.fs.utm.my

Article history :
Received 11 October 2018
Accepted 9 November 2018

GRAPHICAL ABSTRACT



Coumarin

ABSTRACT

Coumarin is a class of compound found abundantly in plants, bacteria and fungi. It is well known for its vast biological activities such as antibacterial, cyclooxygenase inhibition, antimutagenic, scavenging of reactive oxygen species (ROS), anti-inflammatory, anticoagulant, lipoxygenase, CNS stimulants, antithrombotic, vasodilatory, and anticancer activity. In this study, 7-hydroxy-4-methylcoumarin-3-ethyl acetate **1** and its derivatives **2-4** were synthesized. 7-hydroxy-4-methylcoumarin-3-ethyl acetate **1** was synthesized via Pechmann reaction from resorcinol and diethyl acetyl succinate as precursors. Then, several steps of reaction carried out for structural modification of the coumarin were performed. The first reaction is hydrazinolysis of ester group present in coumarin to form 7-hydroxy-4-methylcoumarin-3-acetohydrazide **2**. Further reactions were carried out using Williamson etherification in the presence of potassium carbonate as mild base. The Williamson etherification was carried out by using isobutyl chloride to yield 7-isobutyloxy-4-methylcoumarin-3-ethyl acetate **3**. Similar to the Williamson esterification reaction, 1-chloroacetone was reacted with 7-hydroxy-4-methylcoumarin-3-ethyl acetate **1** to yield O-alkylated product 7-(2-oxopropoxy)-4-methylcoumarin-3-ethyl acetate **4**. The synthesized compounds were characterized using spectroscopic techniques including attenuated total reflection - infrared spectroscopy (ATR-IR) and nuclear magnetic resonance (NMR).

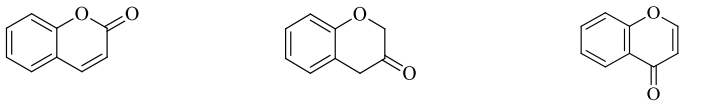
Keywords: coumarin, 7-hydroxycoumarin, Williamson etherification, O-alkylation, hydrazinolysis

1. INTRODUCTION

There are many medicinal compounds being discovered throughout the world. It is important for us to know and appreciate that scientists have learnt to modify or derive the chemical structure of active compounds for improved clinical activity with reduced toxicity [1]. Occurrence of coumarin in various herbal remedies with relatively low toxicity intrigues scientists all around the world to modify the coumarin structures that exist currently [2].

Coumarin or also known as benzopyran-2-one derivatives can be found easily in natural compounds. Since the early stage of studies in 1820s, it has been incurred from more than 800 plant species, and there have been investigations on more than 1000 of its derivatives [3, 4]. Compounds containing coumarin moiety are known for its odour, stability to alkali and availability.

Coumarin is a heterocycle and it belongs to the family of benzopyrones. Heterocycles can involve in a wide range of action types, providing their wide uses in pharmaceutical industry. They can transform themselves to acid or base, depending on pH of the medium. These lead them to interact readily with electrophilic reagents or nucleophiles and sometimes with both [5]. Figure 1 illustrates the structure of coumarins. This research focused on synthesizing and characterizing 7-hydroxy-4-methylcoumarin-3-ethyl acetate **1** and its derivatives **2-4**.



Benzo-α-pyrones (Coumarin) | Benzo-β-pyrones | Benzo-γ-pyrones (Chromones)

Figure 1 Structure of coumarins.

2. EXPERIMENTAL

2.1. Preparation of 7-hydroxy-4-methylcoumarin-3-ethyl acetate **1**

Resorcinol (1.00g, 9.10 mmol) and diethyl acetyl succinate (1.82mL, 9.10 mmol) were stirred in a conical flask placed in ice bath while 80% of sulphuric acid (0.60 mL) was added dropwise to the mixture. The mixture was left to stir overnight at room temperature. Then the reaction mixture was poured to ice bath and the solid formed was filtered off by vacuum filtration. The solid product was then recrystallized using ethanol to obtain desired compound **1**.

Pale brown solid, yield 83.73%, m.p. 258-262 °C, R_f 0.71 in (EtOAc:Hexane, 1:1); ATR ν_{max} cm^{-1}: 3431 (O-H), 3127 (sp^2 C-H), 2983 (sp^3 C-H), 2937 (C-H), 1719 (C=O), 1667 (C=C), 1578-1445 (C=C aromatic), 1186 (C-O); ^{1}H NMR δH (300 MHz, MeOD) ppm: 7.63 (1H, d, J = 8.7 Hz, H-5), 6.82 (1H, q, J = 8.7 Hz, H-6), 6.69 (1H, d, J = 2.1 Hz, H-7), 4.92 (1H, s, -OH), 4.16 (2H, q, J = 14.4 Hz, H-2), 3.68 (2H, s, H-3), 2.39 (3H, s, H-4), and 1.26 (3H, t, J = 7.2 Hz, H-1).

2.2. Preparation of 7-hydroxy-4-methylcoumarin-3-acetohydrazide **2**

7-hydroxy-4-methylcoumarin-3-ethyl acetate **1** (1.05 g, 4.00 mmol) was dissolved in a solution containing ethanol (20.0 mL) and stirred until it formed a homogenous solution. Then 100 % hydrazine hydrate (0.20 mL, 4.00 mmol) was added dropwise and stirred until it formed clear solution. The mixture was then refluxed at 80 °C with stirring for 10 hours. Then, the concentration of the reaction mixture was reduced to half by rotatory evaporator. The solid product formed upon cooling the reaction mixture was separated, collected by suction filtration, washed with ethanol, and recrystallized from ethanol to give 7-hydroxy-4-methylcoumarin-3-acetohydrazide **2**.

Yellow solid, yield 79.63%m.p. 442-446 °C, R_f 0.64 in (EtOAc:MeOH, 1:1); ATR ν_{max} cm^{-1}: 3279 (O-H), 3183 (N-H), 3061 (sp^3 C-H), 1680 (C=O), 1609 (C=C), 1574-1477 (C=C aromatic), and 1351 (C-0) ; ^{1}H NMR δ_H (300 MHz, DMSO) ppm: 9.09 (1H, weak, N-H), 7.63 (1H, d, J = 9.0 Hz, H-3), 6.79 (1H, q, J = 9.0 Hz, H-4), 6.69 (1H, d, J = 1.7 Hz, H-5), 3.61 (1H, br. s, -OH), 2.33 (3H, s, H-2), 1.66 (2H, weak, NH2) and 1.16 (2H, s, H-1).

2.3. Preparation of 7-isobutyloxy-4-methylcoumarin-3-ethyl acetate **3**

Pottasium carbonate, K_2CO_3 was dissolved in ethanol (5 mL) in a round bottom flask. 7-hydroxy-4-methylcoumarin-3-ethyl acetate **1** (0.60 g, 2.3 mmol) was dissolved in ethanol (10 mL) and added to a round bottom flask with K_2CO_3 followed by isobutyl chloride (0.5 mL, 2.3 mmol). The mixture was then refluxed at 100 °C for 24 hours in oil bath. Then, the K_2CO_3 was filtered off and the solution was concentrated using rotatory evaporator. The remaining liquid was refrigerated for 24 hours. 7-isobutyloxy-4-methylcoumarin-3-ethyl acetate **3** formed as solid was collected by vacuum filtration.

Pale orange powder, yield less than 1%, m.p 210-214 °C, R_f 0.68 in (EtOAc:Hexane, 1:1); ATR ν_{max} cm^{-1}: 3125 (aromatic C-H), 2924 (sp^3 C-H), 1720 (C=O), 1669 (C=C), 1580-1446 (C=C aromatic), and 1188 (C-0) ; ^{1}H NMR δ_H (300 MHz, Acetone-D) ppm: 7.68 (1H, d, J = 8.7 Hz, H-5), 6.88 (1H, q, J = 8.7 Hz, H-6), 6.76 (1H, J = 2.4 Hz, d, H-7), 4.12 (2H, q, J = 7.2 Hz, H-2), 3.68 (2H, t, J = 3.3 Hz, H-8), 2.93 (2H, s, H-3), 2.42 (3H, s, H-4), 1.29 (1H, m, H-9), 1.22 (3H, t, J = 7.2 Hz, H-1), and 0.87 (6H, d, J = 5.7 Hz, H-10).

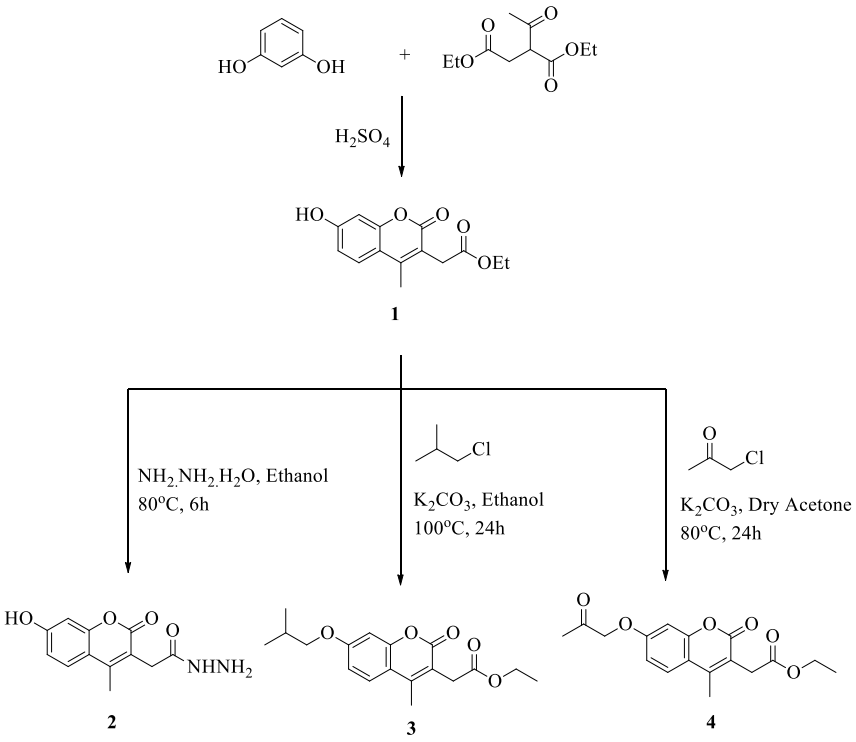
2.4. Preparation of 7-(2-oxopropoxy)-4-methylcoumarin-3-ethyl acetate **4**

In a round bottom flask, 7-hydroxy-4-methylcoumarin-3-ethyl acetate **1** (0.71 g, 2.7 mmol), dry acetone (40 mL), K_2CO_3 (5.0 g) and 1-chloroacetone (0.3 mL) were added and refluxed for 24 hours at 80 °C. The reaction progress and disappearance of the reactants were checked via TLC. Then, the K_2CO_3 was filtered off and the solution were concentrated using rotatory evaporator. Ice water was poured onto the remaining solution. The solid formed was separated off by vacuum filtration. The solid was recrystallized from acetone to give desired product **4**.

Yellow solid, yield 44.93%, m.p. 267-270 °C, R_f 0.79 in (EtOAc:Hexane, 1:1); ATR ν_{max} cm^{-1}: 3102 aromatic C-H), 2976 (sp^3 C-H), 2922 (sp^3 C-H), 1721 (C=O), 1697 (C=O), 1611 (C=C), 1569-1412 (C=C aromatic), and 1150 (C-0); ^{1}H NMR δ_H (300 MHz, CDCl3) ppm: 7.57 (1H, d, J = 9.0 Hz, H-5), 6.90 (1H, q, J = 9.0 Hz, H-6), 6.76 (1H, d, J = 2.4 Hz, H-7), 4.64 (2H, s, H-8) 4.17 (2H, q, J = 7.2 Hz, H-2), , 3.71 (2H, s, H-3), 2.39 (3H, s, H-4), 2.31 (3H, s, H-9), and 1.27 (3H, t, J = 7.2 Hz, H-1).

3. RESULTS AND DISCUSSION

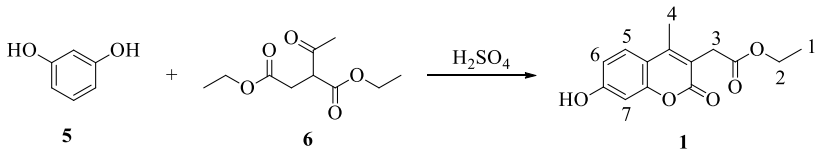
3.1. Synthesis of target compounds



Scheme 1 Synthesis route of 7-hydroxy-4-methylcoumarin-3-ethyl acetate and its derivatives.

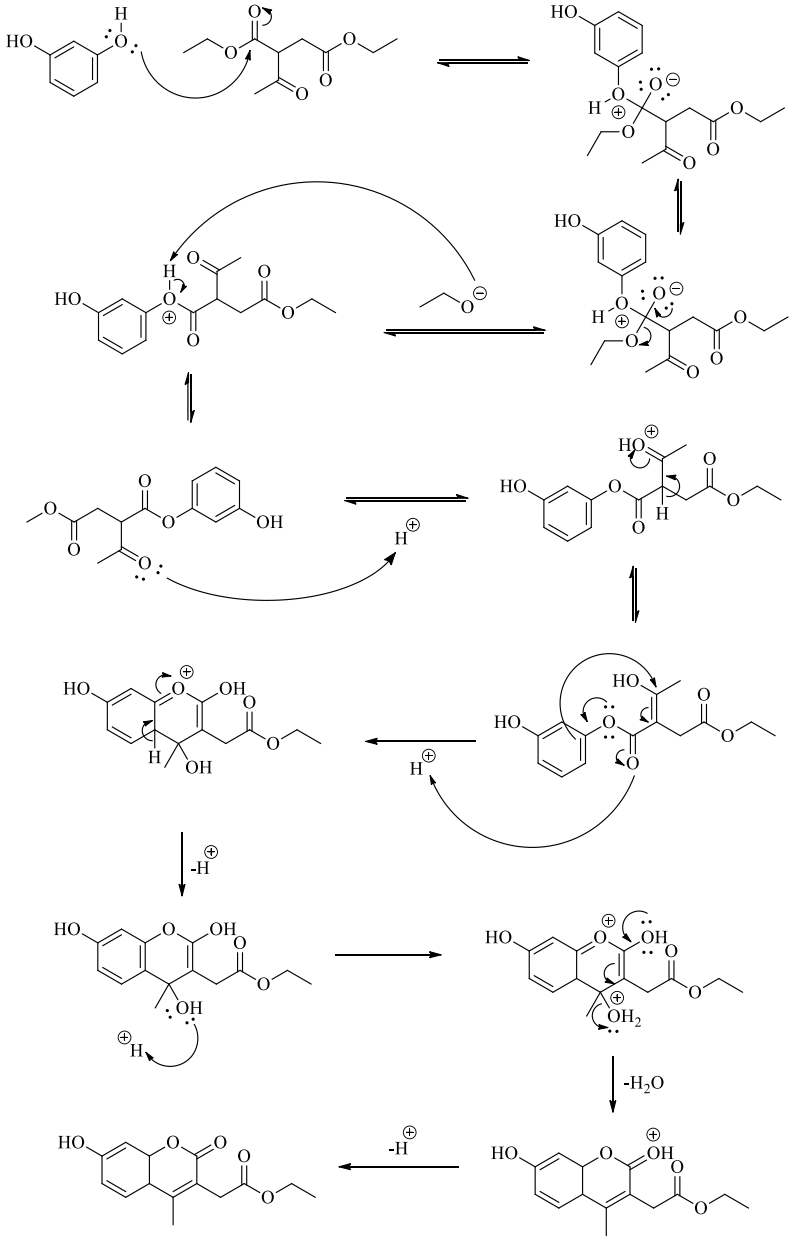
Scheme 1 illustrates the synthesis of 7-hydroxy-4-methylcoumarin-3-ethyl acetate **1** and its derivatives **2-4**. 7-hydroxy-4-methylcoumarin-3-ethyl acetate **1** was synthesized via Pechmann reaction [6] between resorcinol and diethyl acetyl succinate. This compound **1** was then undergo several steps of reactions to yield 3 derivatives **2-4**. First, 7-hydroxy-4-methylcoumarin-3-acetohydrazide **2** was synthesized via hydrazinolysis reaction [7, 8] in the presence of hydrazine hydrate as reagent, K_2CO_3 a mild base and ethanol as solvent. The next derivative **3** was synthesized via Williamson etherification [9, 10] with isobutyl chloride as alkyl halide. Derivative **3** was synthesized in low yield which is less than 1%. This might be overcome by using dipolar active solvents such as DMSO or DMF [11]. Other than that, it might be because of the mixing rate [10]. Low rate of mixing can cause decrease in product yield and increase in reaction time. 7-(2-oxopropoxy)-4-methylcoumarin-3-ethyl acetate **4** was synthesized via a method similar to the Williamson etherification by using 1-chloroacetone.

3.2 Synthesis of 7-hydroxy-4-methylcoumarin-3-ethyl acetate **1**



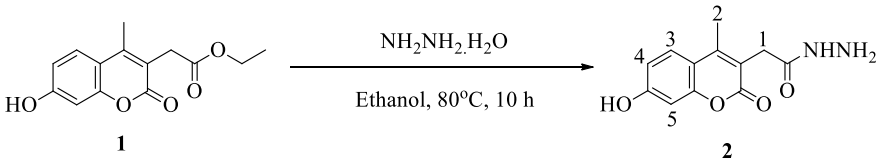
Scheme 2 Method used in this study to synthesis 7-hydroxy-4-methylcoumarin-3-ethyl acetate **(1).**

The Pechmann condensation reaction [6] between resorcinol **5** and diethyl acetyl succinate **6**, a β-ketoester resulted in the formation of 7-hydroxy-4-methylcoumarin-3-ethyl acetate **1**. Pechmann condensation reaction initiated by the attack of hydroxyl oxygen of resorcinol to β-keto carbonyl carbon of diethyl acetyl succinate. It forms a β-ketoester with the release of hydrogen. The compound undergoes keto-enol tautomerisation due to presence of acid catalyst between ester with its enol. The target compound **1** obtained through the Michael Addition reaction followed by acid-induced elimination of water. The mechanism for the formation of compound **1** is shown in Scheme 3.



Scheme 3 The mechanism for formation of compound **1.**

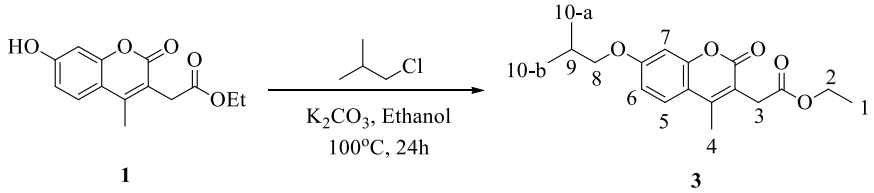
3.3 Synthesis of 7-hydroxy-4-methylcoumarin-3-acetohydrazide **2**



Scheme 4 Method used in this study to synthesize 7-hydroxy-4-methylcoumarin-3-acetohydrazide **2.**

Hydrazynolysis at compound **1** results in hydrazination of ester group to form compound **2** [7, 8]. The ethoxide ion released will react with ethanol to form ester. The mechanism for hydrazynolysis of **1** to form compound **2** is illustrated in scheme 7(a)

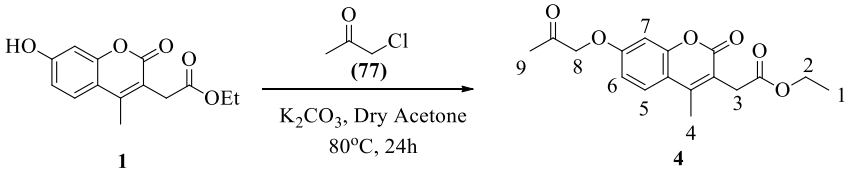
3.4 7-isobutyloxy-4-methylcoumarin-3-ethyl acetate **3**



Scheme 5 Method used in this study to synthesis 7-isobutyloxy-4-methylcoumarin-3-ethyl acetate **3.**

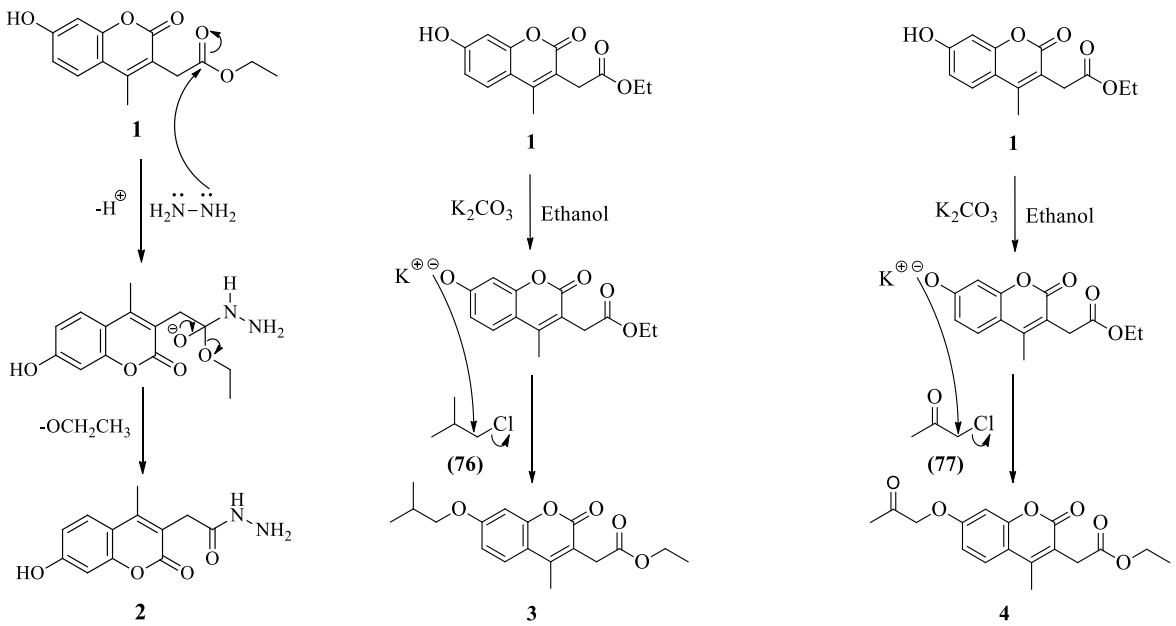
The methylation of coumarin compound **1** with isobutyl chloride, catalysed by base, K_2CO_3 yielded 7-isobutyloxy-4-methylcoumarin-3-ethyl acetate **3**. Nucleophilic bimolecule substitution, S_N2 between a primary alkyl halide and the phenoxide ion took place via Williamson etherification reaction [9, 10]. Phenolic moiety of **1** was changed into phenoxide ion by the reaction with base K_2CO_3. The synthesis of 7-isobutyloxy-4-methylcoumarin-3-ethyl acetate **(74)** gave very poor yield. Polar aprotic solvents such as DMSO, and DMF are recommended to be used with the aid of phase transfer catalysts to give good yield of product [11]. Other than that rate of mixing also plays a vital factor in Williamson etherification. Low rate of mixing causes decrease in product yield and increase in reaction time [10]. The mechanism for the formation of compound **3** is shown in Scheme 7(b).

3.5 7-(2-oxopropoxy)-4-methylcoumarin-3-ethyl acetate **4**



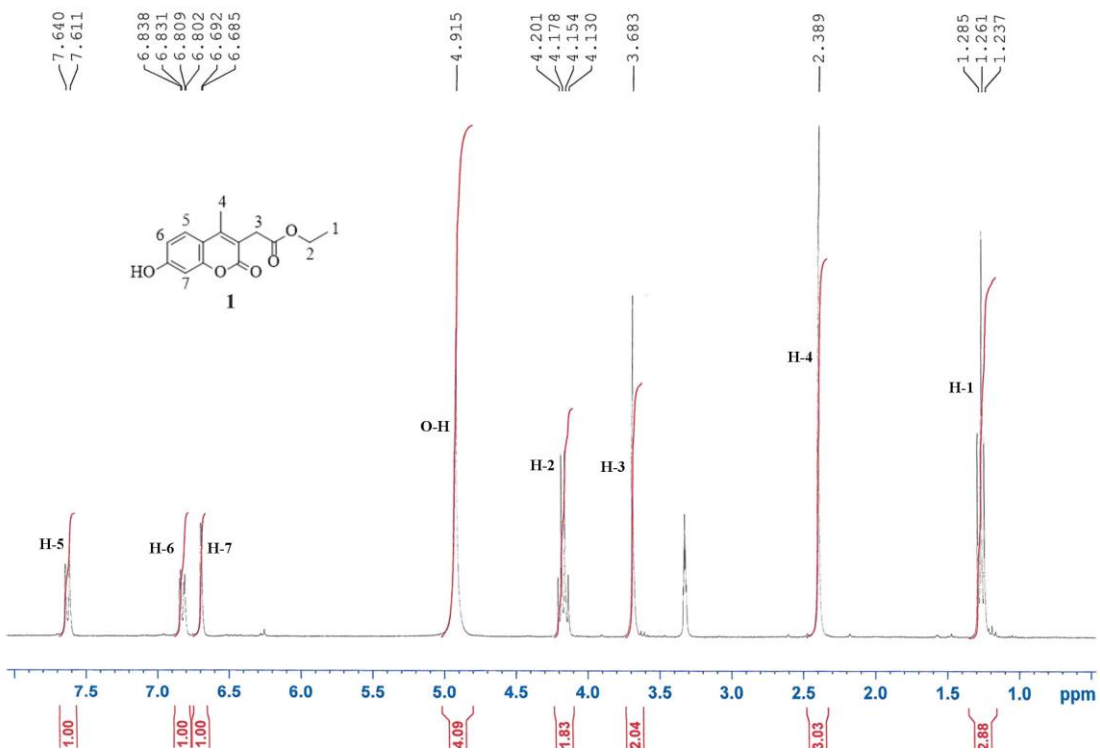
Scheme 6 Method used in this study to synthesis 7-(2-oxopropoxy)-4-methylcoumarin-3-ethyl acetate **4.**

7-hydroxy-4-methylcoumarin-3-ethyl acetate when reacted with 1-chloroacetone, forms 7-(2-oxopropoxy)-4-methylcoumarin-3-ethyl acetate **4**. The compound **4** formed by an S_N2 reaction of phenoxide ion with 1-chloroacetone under basic condition. Under basic condition this O-alkylation reaction [12] gave reasonably good yield. It must be noted that O-alkylation reaction is similar to the Williamson etherification. The mechanism for the formation of compound **4** is shown in Scheme 7(c).

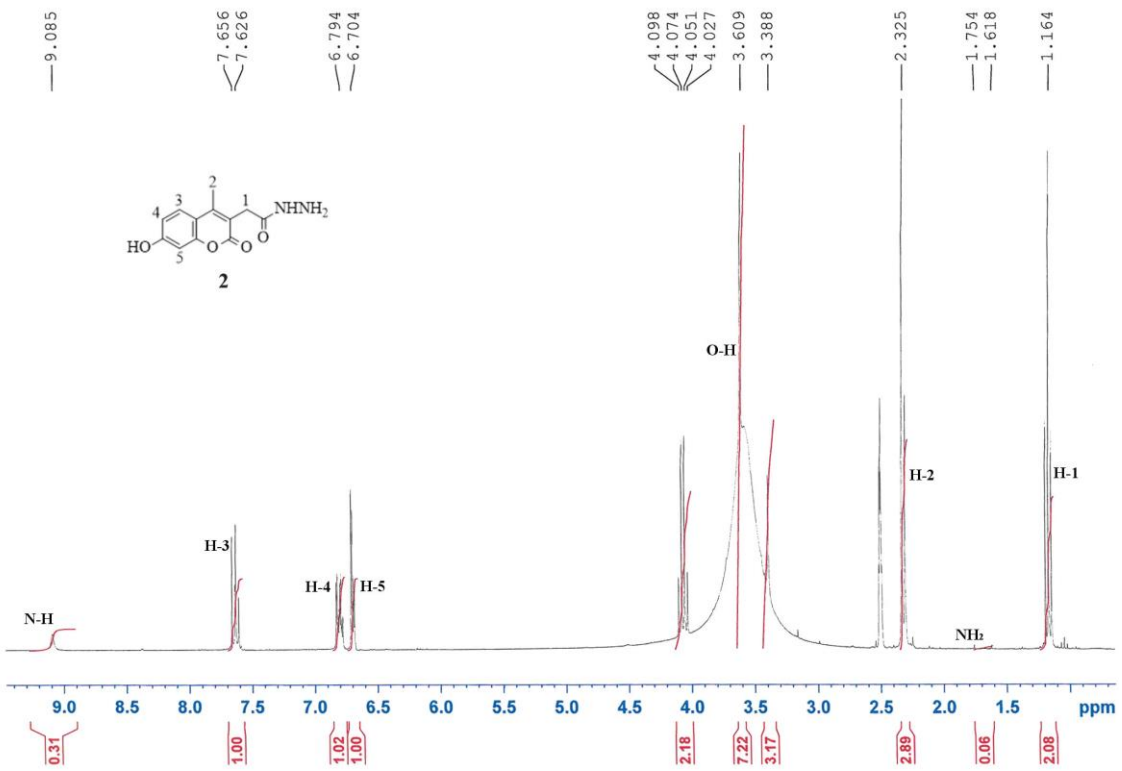


Scheme 7 Mechanism for formation of compounds (a) **2**, (b) **3**, and (c) **4**.

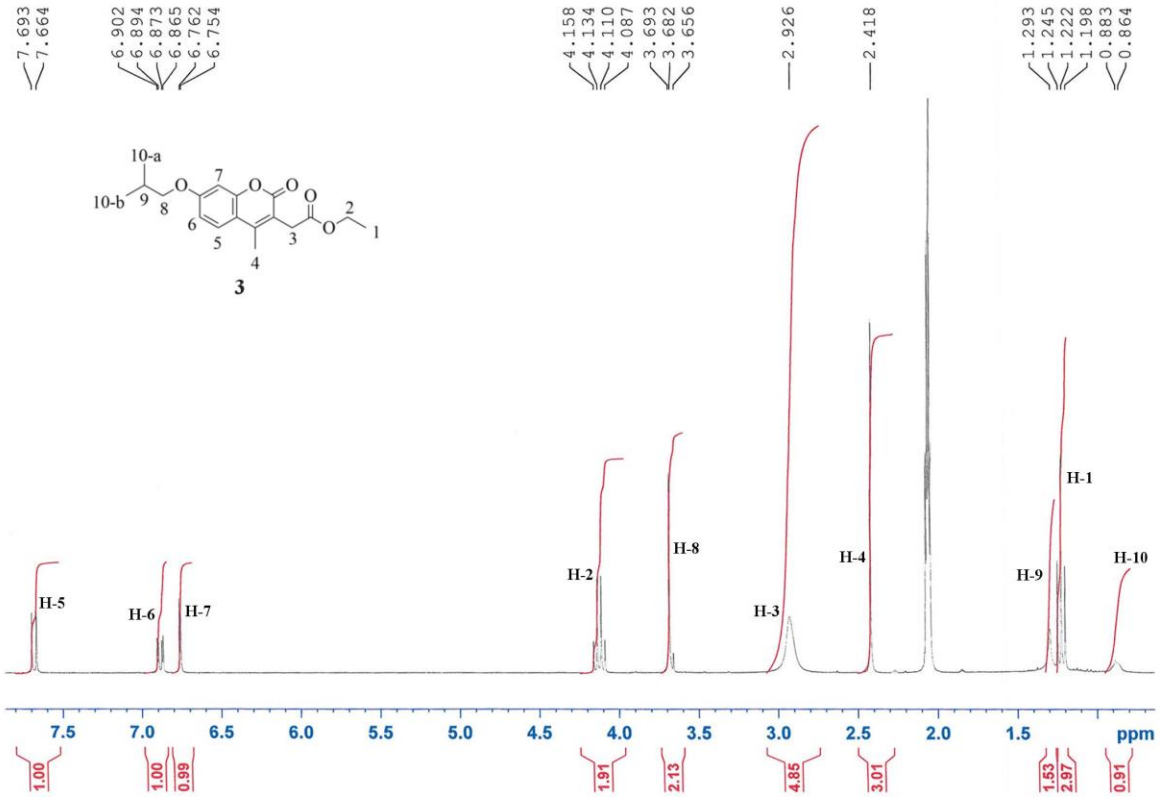
(a)



(b)


9.085
7.656
7.626
6.794
6.704
4.098
4.074
4.051
4.027
3.609
3.388
2.325
1.754
1.618
1.164
NHNH2
HO
O
2
O-H
H-1
H-2
H-3
H-4
H-5
N-H
NH2
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
0.31
1.00
1.02
1.00
2.18
7.22
3.17
2.89
0.06
2.08

(c)


7.693
7.664
6.902
6.894
6.873
6.865
6.762
6.754
4.158
4.134
4.110
4.087
3.693
3.682
3.656
2.926
2.418
1.293
1.245
1.222
1.198
0.883
0.864
10-a
10-b
O
O
O
O
3
H-1
H-2
H-3
H-4
H-5
H-6
H-7
H-8
H-9
H-10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
1.00
0.99
1.91
2.13
4.85
3.01
1.53
2.97
0.91

(d)

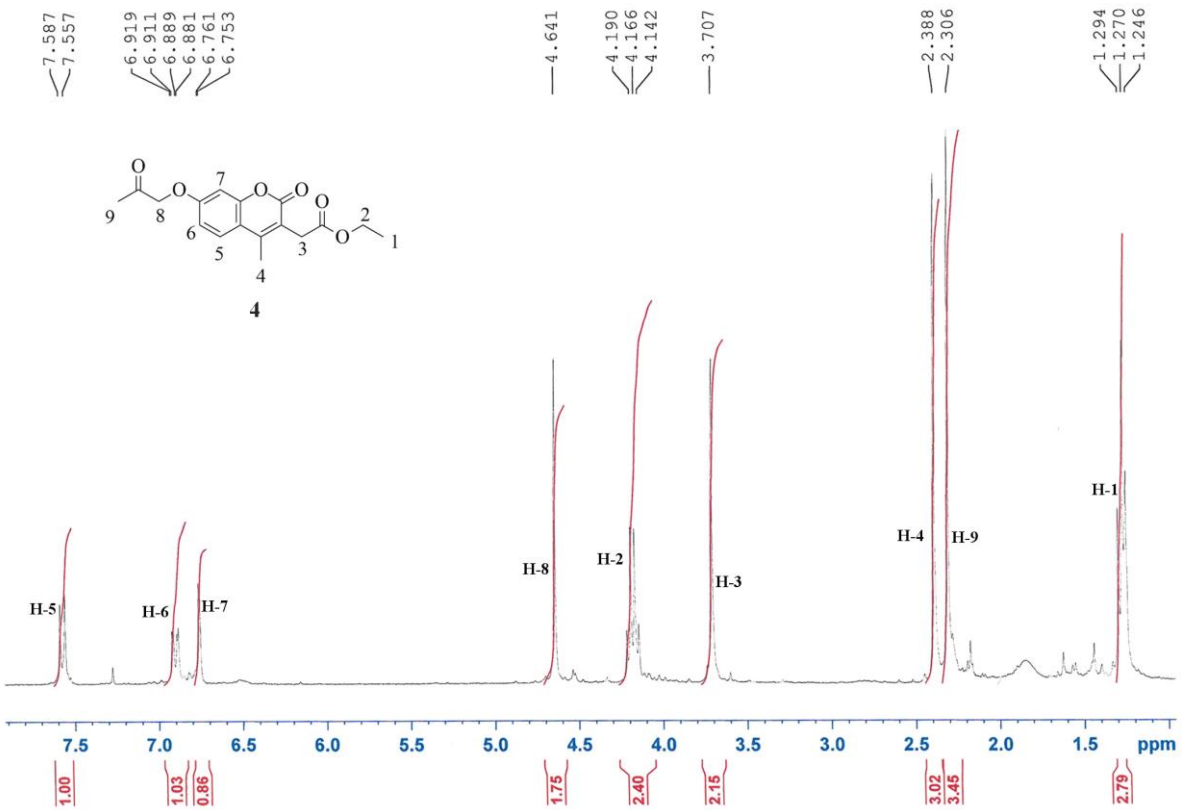


Figure 2 ^{1}H NMR spectrum of (a) **1**, (b) **2**, (c) **3** and (d) **4**.

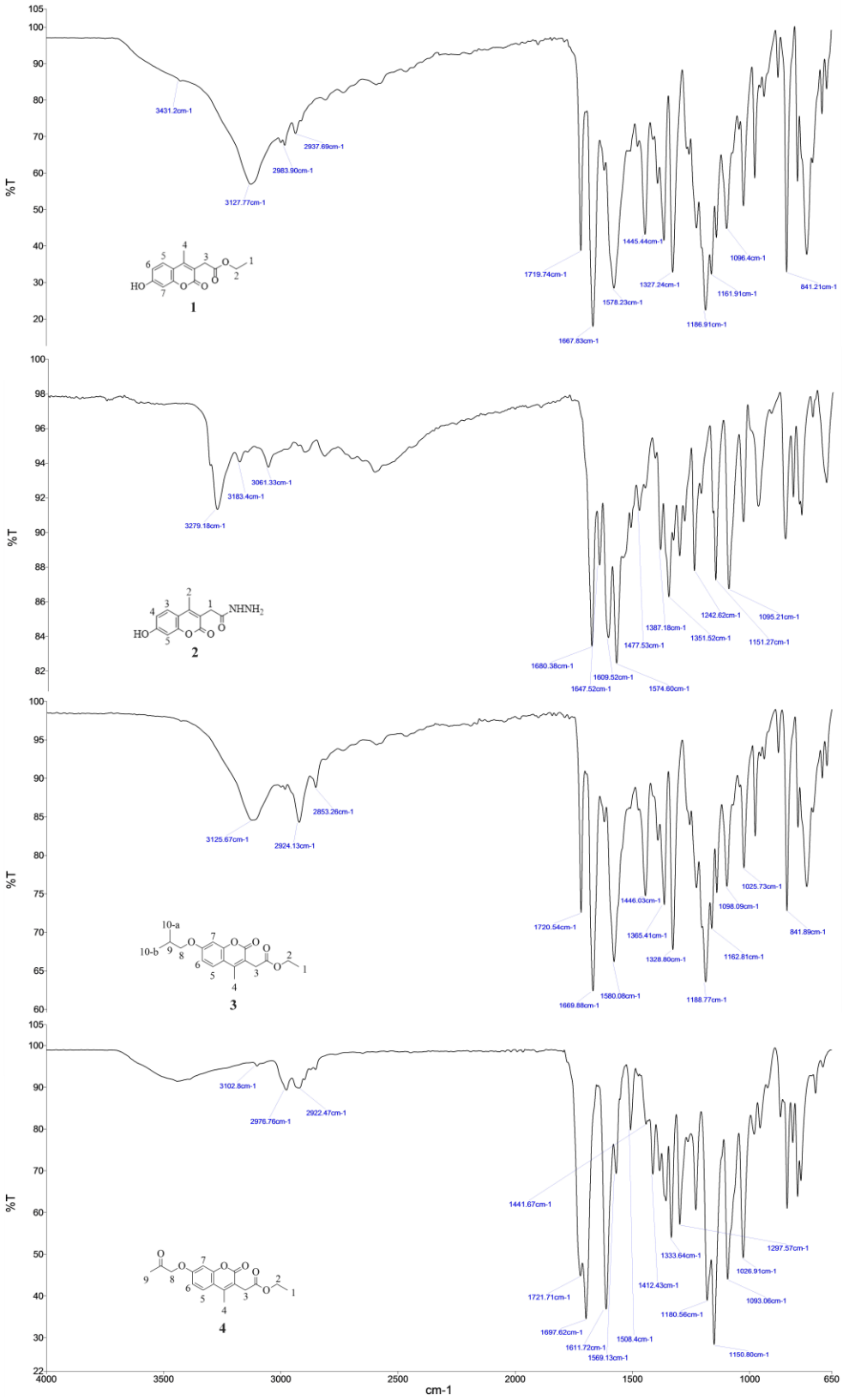


Figure 3 ATR spectrum for **1**, **2**, **3** and **4**.

4. CONCLUSION

7-hydroxy-4-methylcoumarin-3-ethyl acetate **1** was synthesized successfully in 83.73% by Pechmann condensation reaction between resorcinol and diethyl acetyl succinate, a β-keto ester under acidic condition as catalyst. Hydrazinolysis reaction was performed to synthesize 7-hydroxy-4-methylcoumarin-3-acetohydrazide **2** at 79.63% from reaction of 7-hydroxy-4-methylcoumarin-3-ethyl acetate **1** with hydrazine hydrate and ethanol as reagent. Another reaction of Williamson etherification on 7-hydroxy-4-methylcoumarin-3-ethyl acetate **1** gave 7-isobutyloxy-4-methylcoumarin-3-ethyl acetate **3** in very poor yield (<1%). Another reaction that has been carried out is, O-alkylation of 7-hydroxy-4-methylcoumarin-3-ethyl acetate **1** with 1-chloroacetone which gave 7-(2-oxopropoxy)-4-methylcoumarin-3-ethyl acetate **4** in 44.93%.

REFERENCES

[1] Kostova, I. P. (2005). Synthethic and natural coumarins as cytotoxic agents. *Current Medicinal Chemistry - Anti-Cancer Agents*, **5**(1), 28.

[2] Kini, S. G., Choudhary, S., and Mubeen, M. (2012). Synthesis, docking, study, and anticancer, activity of coumarin substituted derivatives of benzothiazole. *Journal of Computational Methods in Molecular Design*, **2**(1), 6.

[3] Venugopala, K. N., Rashmi, V., and Odhav, B. (2013). Review on natural coumarin lead compounds for their pharmacological activity. *BioMed Research International*, **13**, 6.

[4] Gnonlonfin, G. J. B., Sanni, A., and Brimer, L. (2012). Review Scopeletin - A Coumarin Phytoalexin with Medicinal Properties. *Critical Reviews in Plant Sciences*, **31**(1), 10.

[5] Pozharskii, A. F., Soldatenkov, A. T., and Katritzky, A. R. (2011). *An Introduction to Heterocyclic Chemistry, Biochemistry and Applications* (2nd ed. Vol. 2): A John Wiley & Sons, Ltd., Publication.

[6] M.Heravi, M., Khaghaninejad, S., and Mostofi, M. (2014). Chapter One - Pechmann Reaction in the Synthesis of Coumarin Derivatives. *Advances in Heterocyclic Chemistry*, **112**, 50.

[7] Dai, X.-J., and Li, C.-J. (2016). En Route to a Practical Primary Alcohol Deoxygenation. *Journal of American Chemical Society*, **138**, 16.

[8] Cranwell, P. B., Russell, A. T., and Smith, C. D. (2016). Methyl Hydrazinocarboxylate as a Practical Alternative to Hydrazine in the Wolff–Kishner Reaction. *Synlett*, **27**, 5.

[9] Chan, X., Hu, C., Wan, J.-P., and Liu, Y. (2016). Dichloromethane as methylene donor for the one-pot synthesis of bisaryloxy methanes via Williamson etherfication and Suzuki coupling. *Tetrahedron Letters*, **57**, 4.

[10] Massah, A. R., Mosharafian, M., Momeni, A. R., Aliyan, H., and Naghash, H. J. (2007). Solvent-Free Williamson Synthesis: An Efficient, Simple, and Convenient Method for Chemoselective Etherification of Phenols and Bisphenols. *Synthetic Communications*, **37**, 9.

[11] Aspinall, H. C., Greeves, N., Lee, W.-M., Edward G. Melver, and Smith, P. M. (1997). An Improved Williamson Etherification of Hindered Alcohols Promoted by 15-crown-5 and Sodium Hydride. *Tetrahedron Letters*, **38**(26), 4.

[12] Lee, S. C., Lee, S. W., Kim, K. S., Lee, T. J., Kim, D. H., and Kim, J. C. (1998). O-alkylation of phenol derivatives over basic zeolites. *Catalysis Today*, **44**, 6.