Journal of Academia Vol. 9, Issue 1 (2021) 80 – 84

A CONVENIENT SYNTHESIS OF 5-ARYLIDENE MELDRUM'S ACID DERIVATIVES VIA KNOEVENAGEL CONDENSATION

Adryana Izzati Adnan[1], Noor Hidayah Pungot[2] and Nur Ain Nabilah Ash'ari[3]

[1]*Faculty of Applied Sciences, School of Chemistry and Environment, Universiti Teknologi MARA (UiTM), 40450 Shah Alam, Selangor, Malaysia.*
[2, 3]*Organic Synthesis Laboratory, Institute of Science, Universiti Teknologi MARA, Puncak Alam Campus, 43200 Bandar Puncak Alam, Selangor, Malaysia.*

**Corresponding author: noorhidayah977@uitm.edu.my*

Abstract

A series of ten 5-arylidene Meldrum's acid derivatives had been synthesised in excellent yield via Knoevenagel condensation. This method does not require catalyst, or any further purification. Isopropylidene malonate (2,2-dimethyl-1,3-dioxane-4,6-dione), also known as Meldrum's acid, is utilised as a core skeleton for various kind of reactions. Meldrum's acid has features of a peculiar ring-opening sequences based on nucleophile-sensitive carbonyl functional groups at C-4 and C-6, which has made it possible for useful synthetic transformations, as well as its high acidity of methylene hydrogen at carbon position C-5. Hence, it allows the compound to be a flexible reagent for further reaction to prepare other derivatives. Therefore, Meldrum's acid derivatives showed high potential of biological functions, such as antibacterial, antimalarial and antioxidant activities due to the olefinic linkage which played an important role in the enhancement of antimalarial activity. Furthermore, when arylidene Meldrum's acid transformed to epoxide, the compound showed losses of antimalarial behaviour. Additionally, this compound has unique molecules due to the high acidity of methylene hydrogen at the carbon-5 position to initiate various reactions with different functional groups. In this research, Meldrum's acid, **3** and ten its 5-arylidene derivatives **(4a-e)** and **(5a-e)** were synthesised by using two short and efficient reaction steps. The first step involved the condensation of malonic acid, **1** with acetone, **2** in acetic anhydride and acid via one-pot reaction to give Meldrum's acid, **3** in 50% overall yield. Having Meldrum's acid in hand, the reaction was proceeded with the Knoevenagel condensation reaction by using various functional groups, such as aryl aldehydes and aryl amines. All the synthesised compounds were characterised by using ^{1}H and ^{13}C spectroscopy.

Keywords: Biological activities, Knoevenagel condensation, Meldrum's acid, NMR spectroscopy, one-pot reaction

Article History: - Received: 7 November 2020; Accepted: 16 March 2021; Published: 30 April 2021

Introduction

Meldrum's acid was synthesised by a Scottish chemist, Andrew Norman Meldrum. The structure of the product was developed as β-lactone of β-hydroxyisopropylmalonic acid based on the results and acidic properties of the final compound (Lipson & Gorobets, 2009). However, the structure was corrected to be Meldrum's acid in 1948 by Davidson and Benhard's findings. Although, it is nearly 100 years since the discovery of Meldrum acid, it still represents a rather appealing organic synthesis compound. Meldrum's acid, **3** can be prepared by using malonic acid, **1** with acetone, **2** by applying one-pot reaction (Ristovski *et al*., 2018). This technique was suggested by most researchers because the reaction gives a good yield and yet the chemicals used are indeed readily available (Nestrova *et al*., 1994 and McNab, 1978). In recognition of its high acidity, Meldrum's acid could represent as a reagent in Knoevenagel condensation. Knoevenagel condensation reaction is an aldol reaction, whereby carbonyl group in aldehydes and ketones react with active methylene compound that is attached to two electron withdrawing groups to give an alkene. This reaction is practical to form C–C bonds, which is commonly used to facilitate the synthesis of many biologically important compounds and other potential

applications, such as natural products, drugs and polymers (Ferreira *et al.*, 2017). The unique features of Meldrum's acid allow the compound to react with different functional groups such as aromatic aldehydes and amines to give alkylidene derivatives that are useful as key intermediates for diverse types of reactions (Bigi *et al.,* 2001). These alkylidene derivatives are beneficial precursors for cycloaddition reaction and up until recently, previous studies had shown different synthesised derivatives had significant and valuable pharmacological potentials, for examples, antimicrobial, antioxidant and antimalarial activities (Noroozi *et al.,* 2017 and Ristovski *et al.*, 2018). Various approaches were reported to synthesise these derivatives via Knoevenagel condensation, such as by using different condensing agent, namely pyridine, and sodium hydroxide in different solvents, for instance DMSO or DMF under varied controlled conditions (Bigi *et al.,* 2001 and Ghosh *et al.,* 2011). Though, a variety of improvements and changes had been introduced, those approaches had become troublesome as the reaction had caused long reaction time, tedious workflows, poor yield and the need of purification (Pan *et al.*, 2016). Therefore, the objective of this study is to synthesise Meldrum's acid and its derivatives by using a convenient method to give an excellent yield to the target product. In this research, a convenient method was applied as the reactions of 5-arylidene Meldrum's acid involved in one-pot reaction and no purification was needed. Moreover, even though no catalyst was required in the reaction, but most of the derivatives were obtained in higher yield.

Methods

General procedures: All the reagents used were imported from commercial sources. ^{1}H NMR and ^{13}C NMR spectra were determined using Joel Resonance ECZ400S spectrometer at 400 MHz in $CDCl_3$ solution. Chemical shifts were expressed in δ (parts per million (ppm)) units.

Synthesis of Meldrum's acid (3) by Nestrova

To a stirred solution of malonic acid **1** (5.00 g, 48.05 mmol) in 3.88 mL of acetone **2** and 5.7 mL of acetic anhydride was added. The mixture was cooled to 0°- 5°C and 0.14 mL of concentrated sulfuric acid was added drop by drop into the reaction mixture. After the reaction mixture was cooled for 3 hours, 19.6 mL of water was added stages by stages to the resultant precipitate. The mixture was maintained at 0°C for an hour. The completion of reaction was monitored by TLC. The precipitate was filtered off, washed with 30 mL of water and dried it at room temperature to give white solid powder (5.0 g, 50%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.79 (6H, s, 2 x CH_3), 3.64 (2H, s, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 163.0, 106.3, 36.2, 27.6 (Nestrova *et al*., 1994).

General procedure for the synthesis of Meldrum's acid derivatives (4a-e) with aryl aldehydes by Sandhu

To a solution of Meldrum's acid, **3** (0.2 g, 1.39 mmol) and aldehydes (0.21 g, 1.39 mmol), 2 mL of methanol were added. The reaction mixture was stirred at room temperature and the completion of reaction was monitored by TLC in 30 minutes. The solvent was removed to give desired compounds (Sandhu *et al*., 2018).

5-Benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (4a). Yield: 70%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ:1.67 (6H, s, 2 x CH_3), 7.43-7.98 (5H, m, Ar CH), 8.33 (1H, s, CH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.5, 105.1, 112.5, 124.5-135.4, 140.4, 160.8.

2,2-Dimethyl-5-(4-nitrobenzylidene)-1,3-dioxane-4,6-dione (4b). Yield: 94%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ:1.75 (6H, s, 2 x CH_3), 8.01-8.39 (4H, m, Ar CH), 8.46 (1H, s, CH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.5, 105.1, 113.4, 123.8-147.4, 150.1, 161.9.

5-(4-Methoxybenzylidene)-2,2-dioxane-1,3-dioxane-4,6-dione (4c). Yield: 80%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ:1.74 (6H, s, 2 x CH_3), 3.89 (1H, s, OCH_3), 7.01-8.21 (4H, m, Ar CH), 8.33 (1H, s, CH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.5, 56.2, 103.2, 113.4, 119.8-135.6, 150.1, 161.3.

(4-Hydroxy-3-methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (4d). Yield: 90%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ:1.62 (6H, s, 2 x CH_3), 3.79 (1H, s, OCH_3), 7.01-8.13 (3H, m, Ar CH),

8.36 (1H, s, CH), 8.99 (1H, broad s, OH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.5, 50.4, 104.1, 112.8-129.4, 149.2, 150.3, 154.1, 161.3.

5-(4-Ethylbenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (4e). Yield: 45%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ:1.24 (3H, t, CH_3), 1.74 (6H, s, 2 x CH_3), 2.70 (2H, q, CH_2), 7.32-8.02 (4H, m, Ar CH), 8.36 (1H, s, CH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.5, 27.5, 29.4, 103.7, 114.4, 127.8- 143.4, 154.3, 163.4.

General procedure for synthesis of Meldrum's acid derivatives (5a-e) with aryl amine by Sandhu
A mixture of isopropylidene malonate, **3** (0.5 g, 36.0 mmol) in 5 mL of trimethyl orthoformate was refluxed at 202°C for 2 hours. Then, 0.26 mL of aryl amines (0.27 g, 2.88 mmol) was added to the resulting solution and the mixture was refluxed with additional 30 minutes. The crude product was filtered off and washed with methanol to give Meldrum's acid derivatives (Sandhu *et al*., 2018).

2,2-Dimethyl-5-((phenylamino)methylene)-1,3-dioxane-4,6-dione (5a). Yield: 13%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.67 (6H, s, 2CH_3), 7.83-8.34 (5H, m, Ar CH), 8.75 (1H, s, CH), 11.32 (1H, s, NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.8, 104.1, 114.4, 120.8-139.4, 150.1, 164.2.

2,2-Dimethyl-5-(((4-nitrophenyl)amino)methylene)-1,3-dioxane-4,6-dione (5b). Yield: 64%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.65 (6H, s, 2CH_3), 6.93-8.14 (4H, m, Ar CH), 8.54 (1H, s, CH), 12.32 (1H, s, NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.9, 108.2, 114.6, 120.1-138.9, 150.8, 162.7.

5-(((4-Ethylphenyl)aminomethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (5c). Yield: 43%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ: 1.25 (3H, t, CH_3), 1.65 (6H, s, 2 x CH_3), 2.65 (2H, q, CH_2), 6.98-7.27 (4H, m, Ar CH), 8.46 (1H, s, CH), 11.01 (1H, s, NH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ: 14.5, 27.2, 29.2, 104.7, 114.4, 117.8-144.4, 150.3, 165.3.

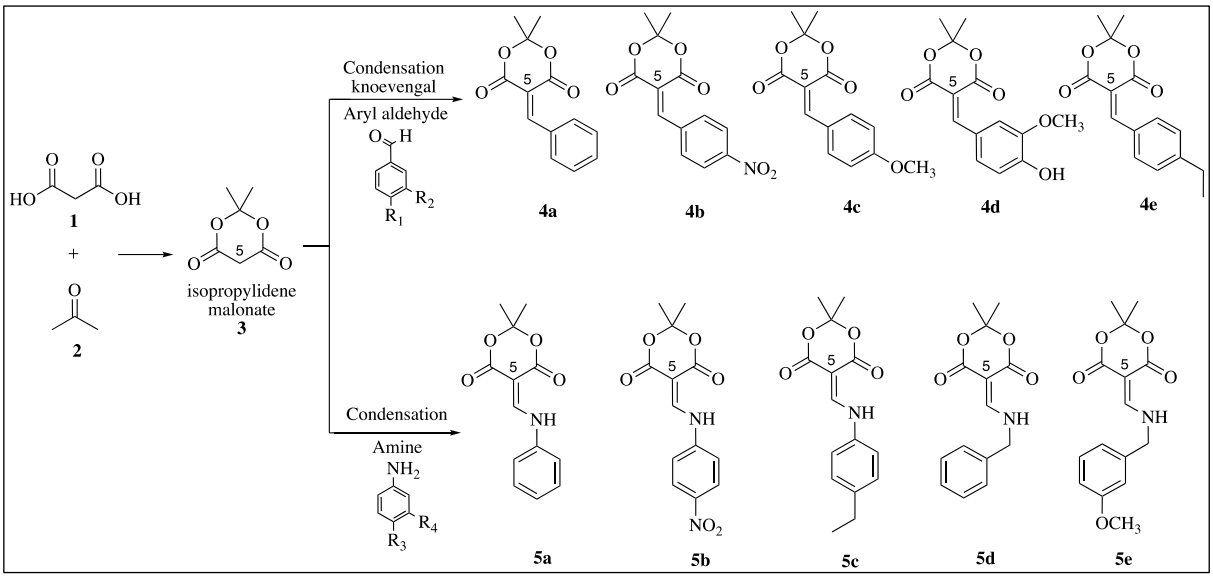
5-Benzylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (5d). Yield: 68%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.65 (6H, s, 2CH_3), 4.59 (2H, s, CH_2), 7.13-7.56 (5H, m, Ar CH), 9.24 (1H, s, CH), 9.56 (1H, s, NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.9, 50.5, 108.2, 126.4-137.9, 140.2, 162.8, 161.7.

5-(((Methoxybenzyl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (5d). Yield: 50%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ: 1.64 (6H, s, 2 x CH_3), 3.72 (1H, s, OCH_3), 4.61 (2H, s, CH_2), 7.08-7.93 (3H, m, Ar CH), 9.36 (1H, s, CH), 9.45 (1H, s, NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.5, 52.4, 56.7, 104.1, 111.8-138.4, 140.2, 161.3, 162.2, 164.3.

Results and Discussions

The synthesis pathway started with condensation of malonic acid, **1** with acetone, **2** in the presence of acetic anhydride and small amount of sulfuric acid via one-pot reaction to give Meldrum's acid, **3** in 50% yield as shown in Figure 1. This technique was uncomplicated and so far the most effective since no catalyst was involved, and further purification was not required. Resulting in the formation of α-protons in Meldrum's acid, **3** that was quite acidic, was therefore ready to response with different functional groups. Correspondingly, **3** was integrated with aryl aldehydes in methanol via Knoevenagel condensation to give 5-arylidene Meldrum's acid derivatives, **4a-e** in 45-94% yield. Another functional group from aryl amine was coupled with **3** in triethyl orthoformate to give **5a-e** with 13-68% overall yield. In this research, 5-arylidene Meldrum's acid with aryl aldehydes showed higher yield compared with aryl amines. This is because aldehyde is a good electrophile, hence less electrons. Therefore, the tendency of nucleophile to attack aldehyde is high which lead to better reactivity and higher yield.

Ten 5-arylidene Meldrum's acid derivatives were successfully synthesised through the Knoevenagel condensation by using different functional groups with an exceptionally good yield. All of these compounds were characterised by using NMR spectroscopy.



Scheme 1. Overall synthetic route of 5-arylidene Meldrum's acid derivatives
Conditions: a) Acetic anhydride, H_2SO_4, 0-5 °C, 3 h, b) Methanol, room temperature, 15-45 min, c) Triethyl orthoformate, reflux, 2 h

Conclusion

In summary, a synthesis of 5-arylidene Meldrum's acid derivatives was accomplished through Knoevenagel condensation in one-pot reactions by using aryl aldehyde and aryl amine functional groups. Based on this finding, higher yield of 5-arylidene Meldrum's acid with aryl aldehydes were obtained in comparison with aryl amines. This was due to the greater reactivity that occurred between the reaction of Meldrum's acid that acted as nucleophile attacks, strong nucleophile which was aryl aldehydes. Meanwhile, 5-arylidene Meldrum's acid with aryl amines showed lower yield due to the presence of electron withdrawing group which was amine, hence, the olefinic linkage was more electrophile. Therefore, the reactivity was unfavourable, giving lower yield of 5-arylidene Meldrum's acid. However, these findings indicated potential future activities of Meldrum's acid derivatives that have not been completely explored. This method had the advantages of optimal reaction conditions, effortless work-up and most significantly, it gave absolutely good yields for the derivatives compounds in comparison to other methods from other findings that had become troublesome to the derivative compounds.

Acknowledgement

The authors are thankful for the financial support of the Institute of Science, [FRGS grant 600-IRMI/FRGS 5/3 (399/2019)], [600-RMC/SRC/5/3 (024/2020)] Universiti Teknologi MARA and assistance with the NMR analysis.

References

Bigi, F., Carloni, S., Ferrari, L., Maggi, R., Mazzacani, A., & Sartori, G. (2001). Clean synthesis in water. Part 2: Uncatalysed condensation reaction of Meldrum's acid and aldehyde. *Tetrahedron Letters, 42*(31), 5203-5205. doi: 10.1016/S0040-4039(01)00978-9

Ferreira, J., de Resende F. J., Batista, P., Teotonio, E., & Vale, J. (2017). Rapid and Efficient Uncatalyzed Knoevenagel Condensations from Binary Mixture of Ethanol and Water. *Journal of the Brazilian Chemical Society, 29*(7), 1382-1387.doi: 10.21577/0103-5053.20170240

Ghosh, S., Das, J., & Chattopadhyay, S. (2011). A novel light induced Knoevenagel condensation of Meldrum's acid with aromatic aldehydes in aqueous ethanol. *Tetrahedron letters, 52*(22), 2869-2872. doi:10.1016/j.tetlet.2011.03.123

Lipson, V. V., & Gorobets, N. Y. (2009). One hundred years of Meldrum's acid: Advances in the synthesis of pyridine and pyrimidine derivatives. *Molecular diversity, 13*(4), 399-419. doi:10.1007/s11030-009-9136-x

McNab, H. (1978). Meldrum's Acid. *Chemical Society Reviews* (3): 345-358.

Noroozi, P. N., Gharib, A., Behroozi, M., & Shokr, A. (2017). New full-substituted cyclopropanes derived from the one-pot reaction of Meldrum's acid with aldehydes and BrCN in the presence of Et_3N. *Arabian Journal of Chemistry, 10*, S1558-S1566. doi:10.1016/j.arabjc.2013.05.024

Nestrova, I. N., Shanazarov, A. K., Poznyak, A. M., Lakoza, M. I., Shemaryankin, B. V., & Granik, V. G. (1994). Improved Method of Synthesizing 2,2-Dimethyl-4,6-Dioxo-1,3-Dioxane (Meldrum's Acid). *Pharmaceutical Chemistry Journal, 28*(8), 583-585. doi: 10.1007/BF02219035

Pan, W. Y., Xiao, Y. M., Xiong, H. Q., & Lü, C. W. (2016). Et 3 N catalyzed cascade reaction of Meldrum's acid with ortho-hydroxyaryl aldehydes for the synthesis of coumarin-3-carboxylic acids under solvent-less condition. *Research on Chemical Intermediates, 42*(9), 7057-7063. doi:10.1007/s11164-016-2517-8

Ristovski, J. T., Janković, N., Borčić, V., Jain, S., Bugarčić, Z., & Mikov, M. (2018). Evaluation of antimicrobial activity and retention behavior of newly synthesized vanilidene derivatives of Meldrum's acids using QSRR approach. *Journal of pharmaceutical and biomedical analysis, 155,* 42-49. doi: 10.1016/j.jpba.2018.03.038

Sandhu, H. S., Sapra, S., Gupta, M., Nepali, K.., Gautam, R., Yadav, S., Kumar, R., Jachak, S. M., Chugh, M., Suri, O. P., & Dhar, K. L. (2010). Synthesis and biological evaluation of arylidene analogues of Meldrum's acid as a new class of antimalarial and antioxidant agents. *Bioorganic & medicinal chemistry, 18*(15), 5626-5633. doi: 10.1016/j.bmc.2010.06.033