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SYNTHESIS OF 5-ARYLIDENE MELDRUM'S ACID DERIVATIVES VIA ONE POT ISOPROPYLIDENE MALONATE WITH DIFFERENT ARYL (ALDEHDYE AND AMINE)

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ABSTRACT

A series of arylidene Meldrum's acid derivatives at C-5 position were synthesized with excellent yield through Knoevenagel condensation reaction via one pot reaction. This approach is quite convenient and effective as it does not require any catalyst and no further purification needed. Meldrum's acid or its scientific name called (2, 2-dimethyl-1, 3-dioxane-4, 6-dione) has received many tremendous interests from organic researchers. Meldrum's acid has a distinctive ring-opening reaction that enables the compound to be versatile reagent and acts as useful intermediate product to synthesis Meldrum's acid derivatives. Besides, Meldrum's acid has high methylene hydrogen acidity located at C-5. Hence, this unique characteristic of Meldrum's acid allows the molecule to react with various kind of functional groups which include aryl aldehydes and arylamine group. In this research, the synthesis of arylidene of Meldrum's acid through one-pot reactions involved two steps. The first step began with condensation of malonic acid with acetone in acetic anhydride with small quantity of sulfuric acid to produce the core skeleton. The second step was introduced with different of substituents such as aryl aldehydes and arylamine group at position C-5 of Meldrum's acid via Knoevenagel condensation reaction in good yield. All the synthesized Meldrum's acid derivatives were characterized using NMR spectroscopy. Therefore, all the series of arylidene Meldrum's acid derivatives will been explored by using the functional group interconversion reactions for potential of biological screening.

Keywords: meldrum's acid, one-pot reactions, knoevenagel condensation, biological activities

1. INTRODUCTION

Meldrum's acid (Isopropylidene malonate) **3** is relatively common in organic synthesis as an intermediate substance to synthesis heterocyclic compounds from variety functional groups [1]. Meldrum's acid is considered to be resilient due to its peculiar reactivities. This is because of its steric rigidity, strong acidity (pKa=4.97) as well as marked ability to recover acetone [2]. The synthesis of Meldrum's acid can be prepared in a single-pot reactions method and this approach was recommended by most organic researchers because of its effectiveness and the chemicals used are readily reachable [2]. The synthetic approach towards 5-arylidene Meldrum's acid derivatives began with the formation of Meldrum's acid via single pot reactions. Meldrum's acid can be synthesized by condensing malonic acid, **1** with acetone, **2** in acetic anhydride along with small quantity of sulfuric acids [3]. Because of the α-protons of Meldrum's acid position at C-5 are extremely acidic, hence enables the molecule to react with an electrophile to further the reaction [4]. The formation of 5-arylidene Meldrum's acid derivatives, can be

synthesized via one-pot as well through Knoevenagel condensation from various functional groups that consists of aryl amine and aldehyde group. Several synthesized of arylidene Meldrum's acid derivatives are found to have biological activities that include antimalarial, antioxidant and antibacterial activity [5][6]. There are numerous published papers on synthesis of 5-arylidene Meldrum's acid using various kind of methods. 5-arylidene Meldrum's acid, **4** can be prepared by condensation of required amount of any aldehyde group with Meldrum's acid at room temperature [5]. The methodology of heating requires reflux step of 3 hours for 5-arylidene Meldrum's acid, **5** using arylamine group as starting material [6]. This method was applied to all arylamine group and successfully achieved with excellent yields.

2. MATERIAL

All the reagents used were imported from commercial sources. ^{1}H-NMR spectra were determined using Joel Resonance ECZ400S spectrometer at 400 MHz in $CdCl_3$ solutions.

3. EXPERIMENTAL

3.1 General procedure to synthesis Meldrum's acid, 3

Malonic acid, **1** (5.00 g, 48.05 mmol) was dissolved into a mixture of 5.7 mL of acetic anhydride (6.13 g, 60.06 mmol) and 3.88 mL of acetone, **2** (3.07 g, 52.86 mmol) by stirring in 100 mL of round-bottomed flask. The reaction of a mixture was cooled to 0-5 °C. Malonic acid will dissolve completely with spontaneous cooling. After that, 0.14 mL of concentrated sulfuric acid (0.26 g, 2.64 mmol) was added drop by drop into the reaction mixture. The reaction mixture was cooled for 3 hours inside a beaker filled with ice blocks at temperature 0-5 °C. Next, 19.6 mL of water was added 2-3 stages to the resultant precipitate to ensure that the reaction mass temperature does not exceed 0-5 °C. The mixture had been maintained at this temperature for an hour. The precipitate was filtered off, washed with 30 mL of water and Meldrum's acid, **3** in white solid powder was dried at room temperature (5.0 g, 50%)

3.2 General procedure to synthesis Meldrum's acid Derivatives with aryl aldehyde, 4a-e

Meldrum's acid, **3** (0.2 g, 1.39 mmol) and an aldehyde (0.21 g, 1.39 mmol) were added in 2 mL of methanol. The reaction mixture was stirred at room temperature for overnight. The completion of reaction is monitored by TLC in 30 minutes. When the reaction had completed, the solvent was evaporated off by using rotary evaporator to give the desired compounds **4a-e**.

3.3 General procedure to synthesis Meldrum's acid Derivatives with aryl amine, 5a-e.

Meldrum's acid, **3** (0.5 g, 36.0 mmol) was dissolved in 5 mL of trimethyl orthoformate and heated at 202 °C under reflux for 2 hours. Next, 0.26 mL of aryl amine (0.27 g, 2.88 mmol) was added. The process was continued with additional 30 minutes of reflux. The completion of the reaction had completed by monitoring using TLC. The precipitate was filtered off and washed with methanol to obtain the desired compounds **5a-e**.

4. FINDINGS

A sequential one-pot synthesis with two or more starting material was added to the reaction mixture one by one to form a product. The synthesis of targeted compound in one-pot reaction was reported to be an

effective method. In single-pot reaction, Meldrum's acid, **3** was successfully synthesized with overall 50% yield *via* condensation reaction of malonic acid, **1** with acetone, **2** in acetic anhydride along with small amount of sulfuric acids. In the ^{1}H NMR spectrum, one singlet was observed at the chemical shift 1.79 ppm. This peak represents the methyl protons of Meldrum's acid. Due to its symmetric structure, therefore the methyl protons shared the same chemical shift. Hence, this proton appeared as single peak. The chemical shift of methylene hydrogens was found at 3.64 ppm as singlet. Due to the presence of α-protons of Meldrum's acid which is very acidic, hence enables Meldrum's acid to react with various functional group. Meldrum's acid has further the reaction to generate 5-arylidene Meldrum's acid derivatives with different functional groups such as aryl (aldehyde and amine) group *via* Knoevenagel condensation. The synthesis of compounds **4a-e** and **5a-e** could be expressed by a reaction order with specific conditions as shown in Figure 1. All synthesized compounds were characterized using ^{1}H NMR spectral data. Various kind of 5-arylidene Meldrum's acid derivatives were successfully synthesized in 13-90% overall yields.

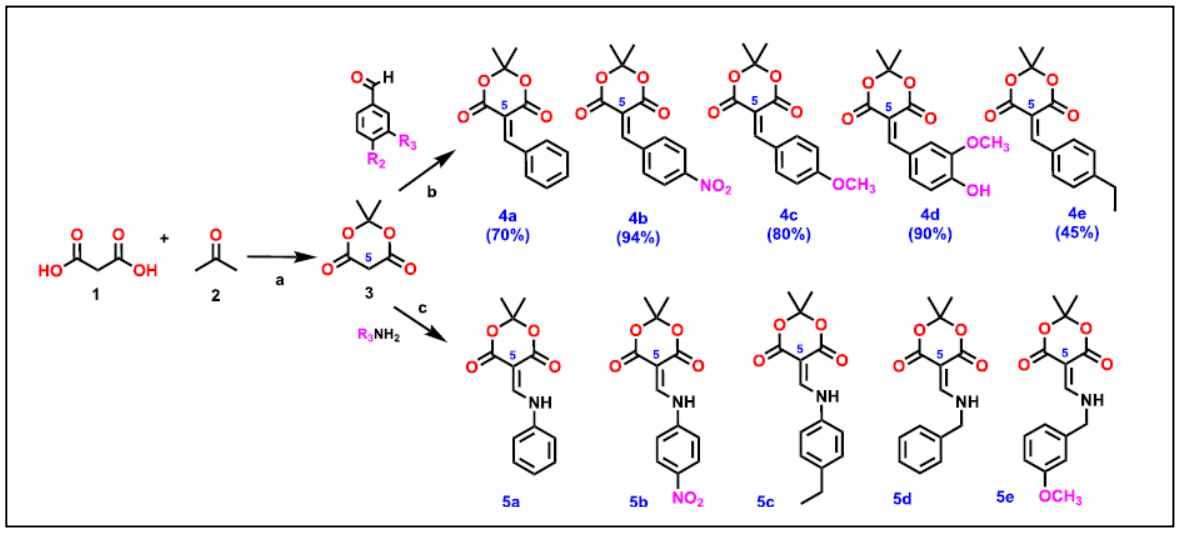

Figure 1. Synthesis of 5-arylidene Meldrum's acid Derivatives.

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

5. CONCLUSION

In summary, an efficient synthesis of 5-arylidene Meldrum acid derivatives were generated *via* Knoevenagel condensation in single pot reaction using various kind of functional group such as aryl aldehyde and aryl amine group. This approach has the benefits of moderate reaction conditions, simple work up and most importantly give an excellent yield to the targeted compounds.

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