Highly efficient one pot synthesis of triacetylphloroglucinol: an analogue of acylphloroglucinol natural product

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Abstract. A green route fast synthesis of triacetylphloroglucinol analogue has been described in detail. This process efficiently achieved by a Friedel-Craft acylation in a one-pot method using phloroglucinol and appropriate acetic anhydride or acyl chloride as acylation agents in the presence of biodegradable catalyst methanesulfonic acid under solvent-free condition. This novel protocol clearly demonstrated green chemistry concept in term of simplicity, good yields and environment-friendly conditions.

1. Introduction
By the virtue of their numerous important applications of phloroglucinol, modification of the phloroglucinol into its derivatives believed to be the one important key to obtain better various compounds. Acylphloroglucinol, one of the important class of phloroglucinol derivatives, has been explored in many fields in recent years [1,2]. Both monoacylphloroglucinol and diacylphloroglucinol derivatives have been investigated and shown potential importance as antimicrobial, enzyme inhibiting, and anti-allergy pharmacological agent [3–8]. On the other hand, triacylphloroglucinols (TAPG), a minor product of secondary metabolite, which is still rarely explored due to its less availability. TAPG is well known of their selective anti-proliferative potential and supported to form some important ligands [8–11]. Based on this reality, some researchers developed various methods to generate TAPG in excellent yield. To only mention recent examples, TAPG has been synthesized using various catalysts such as AlCl₃, BF₃-etherate and ZnCl₂ employing nitrobenzene as the solvent [2,12]. In term of green chemistry, the mentioned catalysts and solvent can be categorized as toxic materials. In addition, these catalysts cannot be easily recovered and recycled. Therefore, there is an urgent need to attempt greener synthetic way to obtain TAPG.

Green chemistry field derived from the increasing request for more sustainable processes in the chemical industry. This concept designed for chemicals processes that aim to eliminate or minimize the use or generation of harmful materials. The use of toxic organic solvents tends to generate waste and consume more energy towards synthesis [13–15]. Chauthe et al [16], proposed a greener way to...
synthesize diacylphloroglucinol (DAPG) using methanesulfonic acid (MSA) catalyst although the DAPG was not the only product a small amount of TAPG was also observed. By adopting green chemistry concepts, we present a new simple green route approach to the preparation of TAPG analogue over biodegradable MSA catalyst. The reaction was designed in one pot step in order to limit the synthetic waste, to spare time, and to simplify practical aspects via the efficiency and environmental sustainability.

2. Experimental

2.1. Materials and Equipment.
All of the reagents were purchased from Merck and Sigma-Aldrich at the greatly commercial quality and directly used without additional purification. The tools used are Infra-red (FT-IR, Prestige 8201 PC, with KBr Pellet), and Nuclear Magnetic Resonance (1H NMR, Agilent 400 MHz). Chemical shifts were reported in parts per million (ppm) relative to the solvent signal for (CD3)2CO (1H NMR; 2.09 ppm). Thin-layer chromatography (TLC) was conducted with TLC Silica gel 60G F254 Glass plates 20 x 20 cm (E-Merck) and visualized by exposure to UV Light (254 nm) or stained with potassium permanganate.

2.2. General Method for the Synthesis of TAPG.
A The synthetic route for the series of TAPG analogues 3 performed previously reported procedures with a slight modification [12]. A flame-dried 10 mL three-necked round bottom flask was charged with phloroglucinol (3 mmol), acetic anhydrides or acyl chlorides (9 mmol) and acetic acid (1.5 mmol) before MSA (9 mmol) was added drop wise at room temperature, stirred 20 min under nitrogen atmosphere and refluxed at 80 °C for 45 min-2 h. The reaction progress was monitored by TLC until the disappearance spot of phloroglucinol. 25 mL of water added to the mixture and allowed to cool at room temperature. The mixture was extracted with ethyl acetate (25 mL). The organic layer was separated and then the aqueous phase was extracted with ethyl acetate (2 × 25 mL) and brine water solution (25 mL), then dried over sodium sulphate anhydrous and concentrated in vacuo to give a crude solid. The resulting crude product was further purified by silica gel (#100–200) column chromatography utilizing eluent the mixture of n-hexane and ethyl acetate (9:1; 8:2; 7:3; and 6:4, respectively) to afford pure product 3, 5a and 5b in 42-72 %.

3. Results and Discussions
In this Herein, the synthetic approach for acetylation of phloroglucinol with acetic anhydride and catalyzed by MSA via Friedel-Craft followed by Fries Rearrangement in acidic condition with short time, high conversions and selectivity, without the use of a solvent is reported. Phloroglucinol (1) constitutes a highly symmetrical and electron rich aromatic system that contains three chemically equivalent active sites that are favourable for electrophilic aromatic substitution reactions. By direct Friedel-Crafts C-acylation, we performed solvent-free acetylation of phloroglucinol via Fries rearrangement of the intermediate O-acetyl derivatives and/or simultaneously both of them as depicted in Figure 1. This synthetic approach is expected as an alternative to substitute the conventional method that still used toxic catalysts, needed longer time, and a large ammount of solvents with relatively high energy intake.

Initially, the reaction investigated at room temperature with acetic anhydride as an acylation agent. Unfortunately, the reaction was incomplete and did not result in the desired product even after 3 h reaction. Carrying out this reaction until 24 h was still not yielding the expected product. TLC analysis showed that the spot of starting material was not completely disappeared even after 24 h reflux. This reaction was controlled by TLC until completion using hexane-ethyl acetate (6:4). In this case, this result proved that solvent-free Friedel-Craft acylation reaction could not be performed at room temperature. Based on previous work [16], the phloroglucinol acylation commonly was done at 80 °C. Thus, in this work, the reaction was then carried out at 80 °C. In order to find optimized condition,
varying the amount of acetic acid and MSA was performed in this reaction via a single step for direct acylation of phloroglucinol.

The direct acylation of phloroglucinol using 1 mol equivalent of acetic acid and 3 mol of MSA was reported by Chauthe et al. [16]. Unfortunately, the TAPG was obtained in lower yield and the reaction tended to give more than 3 products. In the optimum MSA 3 mol, the use of acetic acid less than 0.5 mol equivalent was then investigated and resulted in an incomplete reaction and gave other products such as MAPG and DAPG. In other condition, employing acetic acid more than 1 mol equivalent resulted in TAPG in lower yield followed by MAPG and DAPG. Finally, the use of 0.5 mol equivalent of acetic acid gave the desired product in good yield without MAPG formation although still gave a small amount of DAPG as minor product after 45 minute reaction under a nitrogen atmosphere. By using various solvents such as diethyl ether, chloroform, and diethyl ether also observed in this reaction and did not affect the corresponding target. This is obviously a simple, high yielding and environmentally benign phloroglucinol acylation procedure compared with previous work which uses a toxic catalyst and hazardous solvents. It is clearly differentiating from the other methods which allow the preparation of TAPG with the relatively quick procedure, insignificant waste, and no halogenated constituents.

For the best result, these fascinating initial results prompted us to expand with various TAPG derivatives under raised conditions as outlined in Figure 2.
Figure 2. General reaction one-pot synthesis of triacetylphloroglucinol analogue. Reagent and conditions: (a) acetic anhydride, CH₃COOH, CH₃SO₂OH, 80 °C, 45 min, (b) RCOCl, CH₃COOH, CH₃SO₂OH, 80 °C, 1 h.

Surprisingly, lower yield observed in the presence of bulky acyl group substituents compared to short chain acyl chlorides or acetic anhydride. A stimulating correlation between the size of the acyl chain and the reaction time was observed. By using acetic anhydride and smaller acyl chain, good yield of the products was obtained only in 45 min. These results obviously suggest that the bulk of the acyl chain plays a significant role. A steric hindrance is a possible factor influenced to substitute a benzene ring with three acyl groups. Principally, a reaction with higher atom economy is desirable to one with lower atom economy. This is due to the increasing of atom economy incomes a less waste produced to obtain the desired product. In this work, we found relatively lower value both of the theoretical atom economy (58.34 %) and the experimental atom economy (50.89 %). This indicates that formation of TAPG did not arise easily. However, this method is still gently embedded in green chemistry corridor, because of ability to reduce the reaction time and energy for heating, a small amount of catalyst required and able to eliminate of solvent.

4. Conclusion
In conclusion, a green route fast and convenient method for synthesis TAPG analogue compounds through the direct Friedel-Crafts acylation using a biodegradable MSA catalyst and under solvent-free condition has been developed. This protocol provides a better option because the corresponding reaction afforded in good yield with negligible waste and containing no metallic or halogenated
constituents. The use of a green chemistry concept in this approach because it is believed to be a strategic key to the sustainability of the chemical industry.

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