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Direct Amidation of ethyl *p*-methoxycinnamate to Produce *N,N*-bis-(2-hydroxyethyl)-*p*-methoxycinnamamide

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Abstract

Ethyl *p*-methoxycinnamate (EPMC) (**1**) is found as a major natural ester in the rhizome of *Kaempferia galanga* (kencur) and has been known to have various pharmacological activities. The previous study has reported the synthesis of *N,N*-bis-(2-hydroxyethyl)-*p*-methoxycinnamamide (**2**) by using microwave-assisted direct amidation of EPMC (**1**) with diethanolamine. In this research, we attempt to synthesize of **2** by using a conventional direct amidation of EPMC (**1**) with diethanolamine. The reaction was conducted without adding any coupling reagents or catalyst. Structure of the synthetic product was determined by using analysis of GC-MS, IR, and ^{1}H-NMR spectroscopic data and then compared to the previously reported.

Keywords: Direct amidation, Ethyl *p*-methoxycinnamate, *N,N*-bis-(2-hydroxyethyl)-*p*-methoxycinnamamide.

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1. INTRODUCTION

Ethyl *p*-methoxycinnamate (EPMC) (**1**) is recognized as a natural ester that is responsible for the aroma and pharmacological activities of the rhizome of *Kaempferia galanga* (kencur) (Komala *et al*., 2017; Umar *et al*., 2012, 2014a). For a long time, the rhizome *of K. galanga* has been used as a food flavoring and herbal drink in Indonesia. The herbal drink "beras kencur" which contain *K. galanga* as one of its ingredients is believed to be usefull in increasing appetite and reducing stiffness and pain in the joints or muscles.

Amides are ubiquitous in both natural and synthetic molecules. They are present in the protein, peptides, and certain drug molecules such as an antibiotic, antidepressant, anti-inflammatory, antihypertensive, anticancer etc. (Ghose *et al.*, 1999). Amides are generally prepared from the carboxylic acid moiety and amines in the presence of coupling reagents (De Figueiredo *et al.*, 2016; Joullie and Lassen, 2010).

Direct amidation of esters with amines is one of the alternative routes that can be used in order to synthesize of amide compound. This reaction typically requires stoichiometric amounts of reagents (Kim *et al*., 2012; Vrijdag *et al*., 2014) and catalytic protocols (Morimoto *et al.*, 2014; Caldwell *et al*., 2015). Aminolysis of the ester is attractive in organic synthesis due to the reaction is simple which was supported by stability and easily accessible of starting material (Vrijdag *et al*., 2014).

Previously, we have conducted a microwave-assisted direct amidation of EPMC (**1**) with diethanolamine and ethanolamine to obtain *N,N*-bis-(2-hydroxyethyl)-*p*-methoxycinnamamide (**2)** (92.2% yield) and N-(2-hydroxyethyl)-*p*-methoxycinnamamide (**3**) (61.3 % yield), respectively. Neither coupling reagent nor catalyst was added in this reaction. Both of these cinnamamides have been reported to have interesting anti-inflammatory activity (Komala *et al*., 2017). In another report, a conventional amidation of cinnamoyl chloride with diethanolamine has

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also success to obtain compound **2** *(*Hedvati *et al.*, 2002).

We have a considerable interest in the development of the easy method in the synthesis of the cinnamamides. In this paper, we report the conventional direct amidation of EPMC (**1**) with diethanolamine in order to synthesize of compound **2.** This method has never been reported previously. Furthermore, method and result of the reaction are compared to the previously microwave-assisted direct amidation method.

2. MATERIAL AND METHODS

General experiment

Melting point was measured by using melting point apparatus Stuart SMP10 without correction. IR spectra were recorded on a Shimadzu FTIR Prestige-21. Analysis GC-MS was carried out by using GC/MS-MSD 7890A/5975C (Agilent Technologies) under the following conditions: HP-5MS capillary column (30 m x 0.25 mm ID, 0.25 µm, film thickness) held at 70^{o}C for 2 mins, raised to 285^{o}C, at rate of 20^{o}C/min and held for 20 mins, 285^{o}C for MSD, carrier helium at a flow rate 1.2 mL/min. The ^{1}H-NMR were measured on Jeol-500 MHz instruments. Chemical shift values were expressed in δ (ppm) downfield from TMS as an internal standard.

Plant Collection

The rhizome of *K. galanga* was collected from BALITRO (Balai Penelitian Obat dan Rempah) Bogor, West Java, Indonesia in August 2014 and identified at Bogoriense Herbarium, Research Center for Biology, Indonesian Institute of Sciences, Indonesia.

Extraction and Isolation of EPMC (1)

Extraction and isolation of EPMC (**1**) from the rhizome of *K. galanga* was carried out in accordance with our previous report to give colorless crystal of EPMC (**1**), m.p. 50 °C (Komala *et al*., 2017).

Amidation of EPMC (1) to give *N,N*-bis-(2-hydroxyethyl)-*p*-methoxycinnamamide (2)

In Erlenmeyer flask, the solution of 8.06 g of EPMC (**1**) and 215 mL of diethanolamine was stirred and heated at 200 °C for 2 hours to produce a yellowish-colored viscous liquid. The product of synthesis was then extracted by using *n*-hexane to give 1.62 g of *N,N*-bis-(2-hydroxyethyl)-*p*-methoxycinnamamide (**2**) (20.1 % yield). mp: 84-85°C, GCMS (*m/z*): 265 $[M]^{+}$, 220, 161 (base peak), 133, 90, 63, 42. FTIR(KBr): 3273, 1639, 1604, 1512, 1435, 1365, 1286 cm^{-1}, ^{1}H-NMR (500 MHz, CD_3OD): 3.62 (2H, *t*), 3.73 (2H, *t*), 3.76 (4H, *t*), 3.82 (3H, *s*), 6.94 (2H, *d*, *J*=8.5 Hz), 7.01 (1H, *d*, *J*=15.6 Hz), 7.54 (1 H, *d*, *J*=15.6 Hz), 7.56 (2H, *d*, *J*=8.5 Hz). All of the spectroscopic data are in agreement with those of previously reported (Hedvati *et al.*, 2002; Komala *et al.*, 2017)

3. RESULT AND DISCUSSION

EPMC (**1**) is found as a major ester and easily isolated compound from the rhizome of *K. galanga*. This compound is stable and has been reported to have varied biological activities. Previously we have used this compound as starting material in order to synthesize of various EPMC derivatives and then the anti-inflammatory activity of the synthetic product was evaluated (Komala *et al*., 2017a, 2018b). One of the interesting products of that reaction was *N,N*-bis-(2-hydroxyethyl)-*p*-methoxycinnamate (**2**) which was formed as a result of microwave-assisted direct amidation of EPMC (**1**) with diethanolamine (Komala *et al*., 2017).

In this study, we performed a conventional direct amidation of EPMC (**1**) with diethanolamine in order to synthesize of compound **2**. The reaction was performed without adding any coupling reagents or catalyst. EPMC (**1**) and diethanolamine was mixed in the Erlenmeyer flask, then stirred and heated by using the hot plate at 200 °C for 2 hours to give compound **2** in 20.1 % yields. Scheme of the reaction was shown in Figure 1.

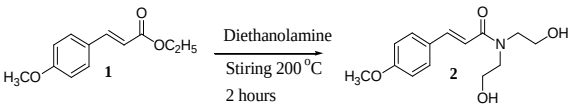

Figure 1. Conversion of EPMC (**1**) to **2**

Compound **2** was obtained as a pale yellow amorphous solid with melting point 84-85°C. The MS data of GCMS showed a molecular ion peak at m/z 265 $[M^{+}]$, corresponding to the molecular formula

$C_{14}H_{19}NO_4$.The prominent peak at m/z 161 indicated the loosing of -$N(C_2H_4OH)_2$ from the structure of compound **2** (Komala *et al*., 2017). The IR spectrum indicated the presence of carbonyl and hydroxyl groups which were appeared at 1639 and 3273 cm^{-1}, respectively.

The ^{1}H-NMR spectrum indicated the presence of two doublet peaks at δ 6.94 (2H, *d*, *J*=8.5 Hz) and 7.56 (2H, *d*, *J*=8.5 Hz); two trans-coupled protons at δ 7.01 (1H, *d*, *J*=15.6 Hz), 7.54 (1H, *d*, *J*=15.6) and a methoxyl group at 3.82 (3H, *s*). The signal patterns described above suggested that this molecule have a *trans*-configuration of the *p*-methoxycinnamate moiety. The remains peaks at δ 3.62 (2H, *t*), 3.73 (2H, *t*), 3.76 (4H, *t*) indicated the presence of –$N(CH_2$-CH_2-$OH)_2$ moiety. All of the spectroscopic data of compound **2** are in agreement with those of previously reported, therefore it confirmed that compound **2** is *N*,*N*-bis-(2-hydroxyethyl)-*p*-methoxycinnamate (Hedvati *et al*., 2002; Komala *et al*., 2017)

Comparison with The Previous Method

Compared to the microwave-assisted direct amidation, conventional direct amidation gave a lower yield and longer time of reaction. Direct amidation of esters with amines typically requires stoichiometric amounts of promoters or metal mediators (Cheung *et al.*, 2017). In our present and previous worked, direct amidation of ester by using both conventional and microwave assisted was performed without adding coupling reagent or catalyst. The use of microwave synthesis reaction has been reported to be often lead a reducing the reaction time, increase yield and easily reaction method (Komala *et al*., 2017, 2018a; Li *et al.*, 2009). So, it is not surprising that the direct amidation by using irradiation microwave gave a good result than the conventional reaction

Nevertheless, the microwave-assisted direct amidation has a limitation such as a) requiring specific equipment (microwave oven), b) there are a certain chemical or solvent that can be used in the microwave-assisted reaction, c) especially when using unmodified microwave oven, the amount of samples that can be used in the single reaction is very limited. Even though conventional direct amidation produce low yield and longer time of reaction, but we can illustrate the advantages of this method compared to microwave-assisted direct amidation such as a) need simple equipment, b) more varied chemical and solvent that can be used, c) it is possible to use large amount of sample in a single reaction

4. CONCLUSIONS

Conversion of EPMC (**1**) into *N*,*N*-bis-(2-hydroxyethyl)-*p*-methoxycinnamamide (**2**) is possible to conduct by using conventional direct amidation of ester in high temperature. In order to overcome the low yield of product synthesis, in the future work, it may need to add coupling reagents or catalyst in the reaction.

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