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Synthesis and Characterization of 2-bromo-4,5-dimethoxybenzaldehyde Compound from Veratraldehyde and $KBrO_3$ In Situ

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Abstract: Bromination is an addition reaction of bromo groups in alkene double bounds like benzaldehyde derivatives. Bromination reaction has an important role in the industrial chemistry because of the multifunctionality of organobromide products in various syntheses. However, the use of bromine molecules can be toxic and reactive. An alternative bromination procedure is needed by avoiding directly bromine through an oxidizing agents such as $KBrO_3$. This research aims to carry out synthesis, characterization and scale up study of the compound 2-bromo-4,5-dimethoxybenzaldehyde from veratraldehyde basic material use $KBrO_3$ as a source of in situ bromine. The bromination mechanism in this study used electrophilic aromatic substitution in acidic conditions to produce the gray-white 2-bromo-4,5-dimethoxybenzaldehyde compound with a melting point of 142-144 °C. Scale up study on the compound 2-bromo-4,5-dimethoxybenzaldehyde showed that mass variations on the compound veratraldehyde, namely 0.5; 1.0; 2.0; and 3.0 grams with successive yields of 21.63; 82.03; 69.38; and 69.84%. The synthesis results were characterized using TLC, FTIR, and GC-MS. The FTIR spectrum showed the vibration of the C-Br, C=O, C=C aromatic and C-O ether functional groups. The typical absorption of C-Br shows absorption at a wave number of 1018 cm^{-1}. The mass spectrum showed a molecular ion (M^+) with m/z 244 which corresponds to the target molecule.

Keywords: bromination, 2-bromo-4,5-dimethoxybenzaldehyde, $KBrO_3$, synthesis, veratraldehyde.

Introduction

Halogenation of double bonds is a topic of discussion that is often found in introductory chemistry courses, especially organic chemistry. The addition reactions of halogen groups such as Br, Cl, F and I to other compounds have been compounds widely carried out in various syntheses, such as halogenation of arenes or heteroarenes which are the reactions most commonly used in medicinal chemsitry (Brown & Bostrom, 2016), studies of halogenation mechanism in alkenes and their double bond reactivity (Mazzuca et al., 2023), and ketone groups (Chai et al., 2023). Halogenation of aromatic compounds usually contains bromine or iodine which functions as an important precursor in various synthetic electrophilic transformation (Terrier, 2013). Bromination is the reaction of adding a bromo group to an alkene double bond, such as the double bond in the aromatic ring of benzaldehyde derivatives which called electrophilic aromatic bromination. This reaction is often used to prepare aryl bromides, which are useful intermediates in various organic syntheses (Li et al., 2014). The addition of bromo groups to aromatic compounds is a fundamental reaction in organic chemistry (Verkhov et al., 2023). Organobromide product compounds have important roles in the chemical, food, agricultural and pharmaceutical industries.

Several research literatures on aromatic electrophilic bromination have been found (Criquet et al., 2015; Li et al., 2014; Liang et al., 2018). Bromination techniques have been developed from various starting materials (Saikia et al., 2016) such as the preparation of α,β-dibromocarbonyl

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compounds as vinyl azide precursors (Shirke & Ramasastry, 2017). Aromatic electrophilic bromination has been widely studied in various synthetic methods (Hornbrook et al., 2023; Verkhov et al., 2023; Y. Zhang et al., 2022), both on an academic scale and in applications in the chemical, pharmaceutical, polymer and agricultural industries (Dagani et al., 2002). Bromination as an interconversion of function groups in organic compounds has a strategic role in determining the synthesis of various bioactive compounds. Substituens on the aromatic ring of a compound influences its bioactivity properties. The halogen group has good antibacterial activity (Prasad et al., 2006) such as bromo- substitued chalcone derivative compounds which have inhibitory power against *Bacillus subtilis* and *Escherichia coli* (Fikroh et al., 2020). In addition, curcumin analog compounds with bromo substituents have antidiabetic activity with an IC_{50} of 422 μM (Yuan et al., 2014).

Bromination reactions involve dangerous reagents such as bromine compunds as a source of bromonium ions (electrophiles). The use of bromine molecules is toxic, irritant and reactive. It makes dangerous effect for humans. Alternative bromination procedures with secure and enviromental friendly methods is needed. The bromination process has been developed using salt-based reagents and non-chlorinated solvent systems (Mathieu & Moniz, 2014) which applied green chemistry principles. Several studies have been found by avoiding direct interactions between bromine compounds (Kumar et al., 2012; Schatz, 1996; Q. Zhang et al., 2013). Bromination techniques using the green synthesis concept will provide environmental improvements as a result of industrial chemical processes. This research aims to synthesize benzaldehyde derivative compounds (veratraldehyde) which substituted for bromo groups using the oxidizing agent $KBrO_3$ as a source of in situ bromine and in scale-up studies using several variations in reactant mass through fixed ratios. In this research, the product compound is one of the main building blocks and starting material in organic synthesis, example by carrying out further synthesis to react with other benzaldehyde to form new compounds namely chalcone compounds and asymmetric curcumin analogues. These intermediate compounds are important in the synthesis of new products as candidate compounds whose activity will be tested.

Materials and Methods

Materials

The materials used in this research have pro-analysis quality from Merck. There are veratraldehyde compounds (3,4-dimethoxybenzaldehyde), potassium bromate ($KBrO_3$), sodium thiosulfate ($Na_2S_2O_3$), bromic acid 47% (HBr), glacial acetic acid, ethanol, ethyl acetate, *n*-hexane, thin layer chromatography plat (TLC, silica gel 60 F_{254}) and distilled water.

Instruments

The instrument used in this research were laboratory glassware (Pyrex), magnetic stirrer, hot plate, vacum desicator and analytical balance (Libror EB330 Shimadzu). The instruments have characterization of a melting point determination tool (Electrothermal 9100), infrared spectrophotometer (FTIR, Simadzu Prestige 21), gas chromatography-mass spectrometer (GC-MS, Shimadzu QP 2010S).

Procedures

This bromination synthesis was carried out by reacting 10 mmol of veratraldehyde was put into a round bottom flask. Then 3,3 mmol $KBrO_3$ was added and 5 mL of glacial acetic acid at room temperature. The mixture stirring using a magnetic stirrer and then 1 mL was added HBr (47%) drop by drop. After the dripping is complete, stirring continues for 45 minutes and the reaction was monitored by TLC. After that, the mixture was poured into 50 mL of ice water, stirred for 10 minutes, then $Na_2S_2O_3$ was added until the color changed. The solid formed was filtered using a Buchner filter, washed with cold distilled water and recrystallized with ethanol. The results were dried in a desicator, weighed and analyzed by melting point, TLC, FT-IR spectrometer and GC-MS. Laboratory scale up studies were carried out to

obtain higher percent yields with different reactant mass variations.

Results and Discussion

Synthesis of the compound 2-bromo-4,5-dimethoxybenzaldehyde

The compound 2-bromo-4,5-dimethoxybenzaldehyde has been synthesized by electrophilic aromatic substitution reaction under acidic conditions. When the reaction occurs, H group substitute to Br group in the veratraldehyde ring. The bromonium ion (Br^+) acting as an electrophile received electron pairs from the aromatic ring as a nucleophile. It formed a carbocation in a benzonium ion which unstable. It followed by H atom to form a more stable double bond structure (Carey, 2000).

This synthesis began by reacting veratraldehyde and $KBrO_3$ with a glacial acetic acid catalyst and adding HBr 47% at room temperature for ± 1 hour. This synthesis produced the change of the solution color from yellow to orange. $KBrO_3$ is an oxidizing agent which is a source of bromine from the oxidation of HBr. This reaction occurs in the system (in situ) so that it can prevent the toxic and irritant properties of bromine. Glacial acetic acid has function in the formation of bromonium ions (Br^+) and act as an electrophile. The electrophile will receive an attack from the electron pair in the veratraldehyde compound called a nucleophile. In the first step, the formation of bromine begins, namely by dissolving potassium bromate in water with glacial acid. This step is safer because oxidizing agents such as $KBrO_3$ caused bromine formed from the oxidation of bromic acid in situ or form in the system after the material urdergoes a reaction, thereby avoiding the directly toxic properties of bromine (Br_2). In the second stage, there is the formation of the electrophile bromonium (Br^+) in the presence of acetic acid. In the third step, there is an aromatic electrophile substitution reaction between the bromonium ion as the electrophile and the aldehyde compound (veratraldehyde) as the nucleophile. The veratraldehyde compound (3,4-dimethoxybenzaldehyde) has an electron donor substituent (a methoxy group), so the bromonium ion will enter the ortho or para position to the methoxy group in veratraldehyde. The veratraldehyde compound also has an electron-withdrawing group (the aldehyde group), so the bromonium ion will enter the meta position. Therefore, it is possible that the bromonium ion will enter the ortho position towards the methoxy group because it is a strong activating group (C_3). $Na_2S_2O_3$ solution was added to the mixture until the color changed to remove residual bromine. The addition of cold distilled water was intended to form a precipitate. The mechanism of this bromination reaction was shown in Figure 1.

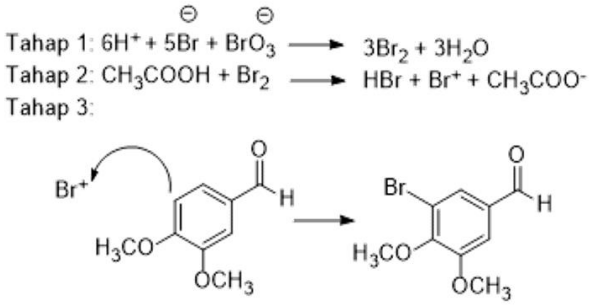

Figure 1. The mechanism of bromination reaction.

The results of the synthesis of the compound 2-bromo-4,5-dimethoxybenxaldehyde were presented in Table 1 and Figure 2.

Table 1. The Synthesis of Product Compound.

Physical Appearance	Synthesis Result
Form	Solids
Color	Grayish white
Melting point	142-144 °C
Percent yield	82,03%

Figure 2. The Synthesis of Product Compound

Thin Layer Chromatography (TLC)

The reaction was monitored with TLC to determine whether the reactants have finished reaction. The synthesized compound was analyzed by TLC using the eluent ethyl acetate:n-hexane (1:1) showing a different R*f* value when compared to veratraldehyde reactant. So it indicates that the product compound has been formed.

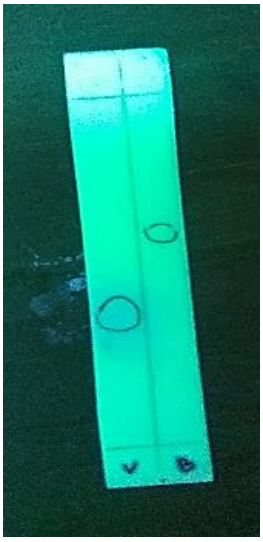

Figure 3. The Result of TLC.

Fourier Transform Infra Red (FTIR)

The analysis used FTIR spectrometer aimed to determine the functional group of the target compound. Based on analysis of FTIR spectrum data, it showed several absorption bands that can be used to identify the presence of target compounds, such as carbonyl groups, aromatic C=C and C-O ether. The vibrational absorption of the C=O group is at wave number 1674 cm^{-1}. The absorption peaks 1589 cm^{-1} and 1504 cm^{-1} is the vibrational absorption of the C=C group on the aromatic ring. The absorption peaks 1273 cm^{-1} and 1157 cm^{-1} is C-O ether absortion and the main absorption band was the appearance of an absorption peak at 1018 cm^{-1} which was the vibration of the C-Br group. It indicated that a bromination reaction has occured and the bromovertraldehyde compound has been formed. This result is similar to the vibration absorption data of the bromo group in the absorption peak of 1057 cm^{-1} (Olivera et al., 2000). It can be concluded that a bromination reaction has occured.

Table 2. FTIR Spectrum Analysis of Product Compounds.

Functional group	Wave number
C=O	1674
C=C aromatic	1589 and 1504
C-O ether	1273 and 1157
C-Br	1018

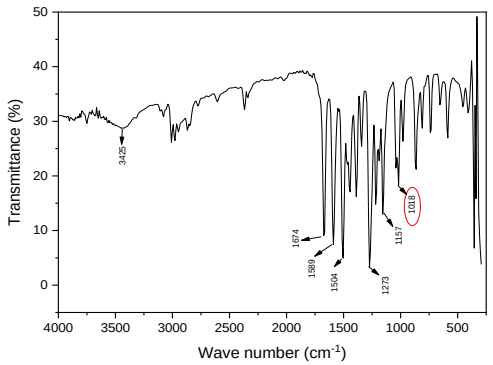

Figure 4. FTIR Spectrum of Compounds.

Gas Chromatography-Mass Spectrometry (GC-MS)

The GC-MS analysis aimed to analyze the number of compounds quantitatively and analyze the molecular structure of the analyte compound. The GC chromatogram showed that there were two peaks, the second peak was the dominant peak with a retention time (tR) of 13.3 minutes and a relative abundance of 85.59%. The first peak had a retention time (tR) of 12.7 minutes and a relative abundance of 14.41% predicted to be the peak of basic material and impurity. Meanwhile, the mass spectrum showed a molecular ion (M^+) with m/z 244 corresponded to the mass of the target molecule. This ion molecular weight corresponds to the molecular weight of 2-bromo-4,5-dimethoxybenzaldehyde with the isotop ^{79}Br so it can be concluded that the bromination reaction has occured.

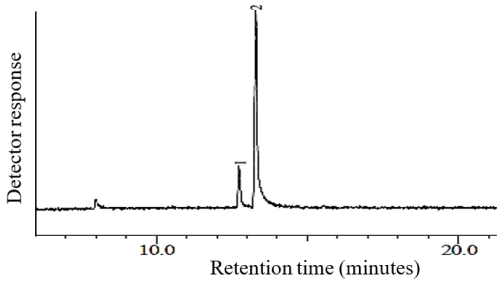

Figure 5. The Result of GC-MS Chromatogram of veratraldehyde bromination.

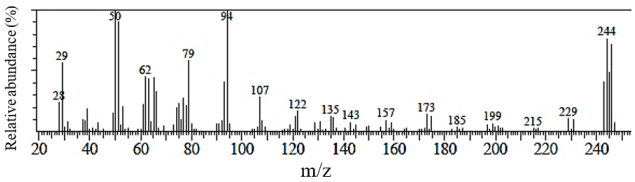

Figure 6. Mass spectrum of peak 2 at t_R = 13,3 minutes

Based on the fragmentation pattern, the m/z 244 molecular ion (M^+) is the base peak releasing –CHO and $–CH_3$ radical to produce two fragments of m/z 215 and 229. The m/z 215 fragment had further fragmentation by releasing $–CH_2O$ molecule and formed an m/z 185 fragment. This compound needs to be further characterized using an ^{1}H-NMR and ^{13}C-NMR spectrometer to confirm the structure of the compound and find out the exact position of the Br atom in the benzaldehyde compound.

Scale Up Study in The Laboratory

This research used several reactant mass variations to obtain the quantity of the bromoveratraldehyde compound as a basic material for the synthesis of the next compound. Therefore, a scale up of the synthesis was carried out in the laboratory by doubling the recipe of the synthesis bromoveratraldehyde compound synthesis procedure. In this study, the mass of veratraldehyde was varied from 0.5; 1.0; 2.0; and 3.0 grams and the results of percent yield were 21.63; 82.03; 69.38; and 69.84% as shown in Table 3.

Table 3. Several Studies Scale Up Recipes for Synthesis.

Mass of veratraldehyde (g)	Volume of HBr	Mass of $KBrO_3$	Volume of glacial acetic acid	Mass of product (g)	Percent yield (%)
0,5	1	0,2	5	0,53	21,63
1	2	0,4	10	1,21	82,03
2	4	0,8	20	2,04	69,38
3	6	1,2	30	3,08	69,84

Based on the results obtained, the amount of product compound was not directly proportional to the amount of reactant. The higher the reactant mass will produce, the higher the percent yield of the product compound should be, if used the same procedures and the same ratio of mole. However, this research does not show the results according to theory, there are several error factors such as inconsistencies in different stirring speeds (the synthesis method was not optimal), improper recrystallization procedures so that the result compound did not yet have 100% purity. The further investigation is needed to get the appropriate and the accurate amount of $Na_2S_2O_3$ which added to remove residual bromine in the solution. The synthesis of the 2-bromo-4,5-dimethoxybenzaldehyde (bromoveratraldehyde) compound has been carried out using $KBrO_3$ to avoid direct use of bromine but a secure method is needed to be developed to minimize waste production.

Conclusions

The compound of 2-bromo-4,5-dimethoxybenzaldehyde can be synthesized through an electrophilic aromatic substitution reaction between veratraldehyde and $KBrO_3$ as a source of bromine to produce a grayish white solid with a yield of 82.03% and a melting point of 142-144 °C. Based on the results of TLC structure elucidation, GC-MS and FTIR showed that the compound 2-bromo-4,5-dimethoxybenzaldehyde had been confirmed.

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Conflict of Interest: The author declare that there are no conflicts of interest concerning the publication of this article.

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