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Formation of Bis(3,5-dichloro-4-hydroxyphenyl)methane From the Reduction of 3,5-Dichloro-4-hydroxybenzoic acid

Ritmaleni[1*] Dion Notario [1,2] Yuliatun[1]

1. Faculty of Pharmacy, Gadjah Mada University, Sekip Utara, Yogyakarta 55281, Indonesia
2. Faculty of Pharmacy, Kampus Unit III, Universitas Sanata Dharma, Paingan, Maguwoharjo, Depok, Yogyakarta 55284, Indonesia

* E-mail of the corresponding author: ritmaleni@ymail.com

Abstract

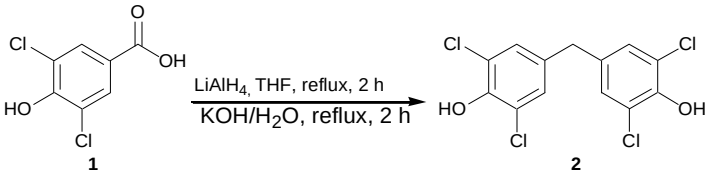
This research was aimed to reduce 3,5-dichloro-4-hydroxybenzoic acid to 3,5-dichloro-4-hydroxybenzyl alcohol by using $LiAlH_4$ as catalyst. Unfortunately, the main product found was different from the normal reduction of carboxylic acid. The obtained product is bis(3,5-dichloro-4-hydroxyphenyl)methane which formed from the cross-linking of the acid. The structure elucidation was carried out based on the spectroscopic analysis method (H-NMR, C-NMR, IR, GC-MS). The product, bis(3,5-dichloro-4-hydroxyphenyl)methane, identified as a brown crystaline solid in 52 % yield.

Keywords: bis(3,5-dichloro-4-hydroxyphenyl)methane, 3,5-dichloro-4-hydroxybenzoic acid, $LiAlH_4$

1. Introduction

The carbonyl group on carboxylic acid is the highest oxidation state of organic molecules. When carboxylic acid is reduced, the product is aldehyde and furthermore can be reduced to alcohol. Lithium Aluminium Hydride ($LiAlH_4$) and Sodium Borohydride ($NaBH_4$) are two of the common reagents to do the reduction. Reduction of carboxylic acids by using $LiAlH_4$ normally form alcohol compounds, such as reduction of α,β-unsaturated carboxylic acids (Jeon *et al*., 2003), heterocyclic carboxylic acids (Jing *et al*., 2009; Powell *et al*., 2000), policyclic carboxylic acids (Okazaki *et al*., 2006), amino acids (Klein *et al*., 2009) and aromatic amino acids (Ritmaleni and Aggarwal, 2011), all form the corresponding alcohol. Carboxylic acids also can be reduced to alcohol by using $NaBH_4/BF_3$ ŦEt_2O. (Cho *et al*., 2004) The reaction mechanisms for both reduction process in reducing carboxylic acids are first change the carboxylic acid to aldehyde and eventually to alcohol (Simek *et al*., 2009; Fox and Whitesell, 2004) and although they are little bit different.

This research was aimed to reduce the 3,5-dichloro-4-hydroxybenzoic acid by using $LiAlH_4$. According to the theory, the reduction was expected to result 3,5-dichloro-4-hydroxybenzyl alcohol. But, the main product obtained in this reaction is bisphenol, bis(3,5-dichloro-4-hydroxyphenyl)methane **2** as an unexpected result from the reaction between a carboxylic compound and a reducing agent.



Scheme 1 Reaction between acid 3,5-dichloro-4-hydroxybenzoic acid **1** and $LiAlH_4$

This molecule which has 3,5-dichloro-4-hydroxy on its aromatic rings, could be possibly has a biological activity as antibacterial agent like PGV-6 **14**, HGV-6 **15**, and GVT-6 **16**. (Sardjiman *et al*., 1997) PGV-6 **14**, HGV-6 **15**, and GVT-6 **16** are three kinds of curcumin analogs that published and patented by faculty of Pharmacy, Gadjah Mada University, Indonesia. Some publications also reported that some similar compounds of bis(3,5-dichloro-4-hydroxyphenyl)methane have antibacterial and antifungi activities to environment. (Wendel, 1957; Mayur *et al*., 1991) as cited by Verhagen *et al*. (1998).

2. Experiment

2.1 Reduction of 3,5-dichloro-4-hydroxybenzoic acid by using $LiAlH_4$ to the formation of bis(3,5-dichloro-4-hydroxyphenyl)methane **2**

To a stirred suspension of $LiAlH_4$ (40 mmol, 1.4 g) in dry THF (15 mL) in three necks round bottom flask was added 3,5-Dichloro-4-hydroxybenzoic acid **1** (10 mmol, 2 g) dropwise in THF (7 mL). The reaction mixture was heated to reflux at 80 ^oC for 2 hours. After cooling down, KOH (264,6 mg; 40 mL in 5 mL H_2O) was added. The reaction mixture was heated to reflux for 2 hours and filtered through celite. The solvent was evaporated under vacuum. The product was isolated from the crude product by using flash column chromatography ($CHCl_3$: MeOH; 2:1) and recrystalised from EtOH/H_2O to yield a brown crystalline bisphenol, bis(3,5-dichloro-4-hydroxyphenyl)methane **2** (864,5 mg, 52 %), R_f ($CHCl_3$:MeOH; 2:1) 0.74, m.p 165-167 ^oC (EtOH/H_2O) ν_{max} (KBr)/cm^{-1} 2930 (C-H), 2853 (C-H); ^{1}H-NMR (500 MHz; $CDCl_3$) 3.74 (2H, s, -CH_2-) [Lit. Verhagen *et al*., 1998; 3.85 (s, 2H, -CH_2-)], 7.04 (4H, s, -Ar-H; ^{13}C-NMR (125 MHz; $CDCl_3$) 39.45 (t); 121.35 (d); 128.63 (s); 133 (s); 146.67 (s); *m/z* (EI) 335,9 (57,4 %); 300,9 (100 %); 265,0 (16,4 %); 231,0 (36.1%); 202,0 (16,4 %); 175,0 (19,7 %); 139,0 (14,6 %); 101,0 (18,8 %); 75 (24,6 %); 51,0 (8,2 %).

2.2. Optimisation of mole equivalent of 3,5-dichloro-4-hydroxybenzoic acid and $LiAlH_4$ used in the synthesis

As method above, using 3,5-Dichloro-4-hydroxybenzoic acid (5 mmol) and $LiAlH_4$ (20 mmol); 3,5-dichloro-4-hydroxybenzoic acid (5 mmol) and $LiAlH_4$ (10 mmol); 3,5-dichloro-4-hydroxybenzoic acid (5 mmol) and $LiAlH_4$ (5 mmol); 3,5-Dichloro-4-hydroxybenzoic acid (5 mmol) and $LiAlH_4$ (2.5 mmol); 3,5-Dichloro-4-hydroxybenzoic acid (5 mmol) and $LiAlH_4$ (1.25 mmol). The process was exactly the same and the compound obtained was also the same according to R_f, m.p. and spectroscopic data.

Table 1. Mole equivalent of 3,5-Dichloro-4-hydroxybenzoic acid **1** and $LiAlH_4$

Acid (mole eq.)	$LiAlH_4$ (mole eq.)	Yield (%)
1	4	52
1	2	26
1	1	11
1	0.25	4

3. Result and Discussion

3.1. Reduction of 3,5-dichloro-4-hydroxybenzoic acid by using $LiAlH_4$ to the formation of bis(3,5-dichloro-4-hydroxyphenyl)methane **2**

The main product was obtained as a brown crystalline solid **2** and its structure has been elucidated by spectroscopic method. From the spectroscopic data the structure identified as bis(3,5-dichloro-4-hydroxyphenyl)methane **2**.

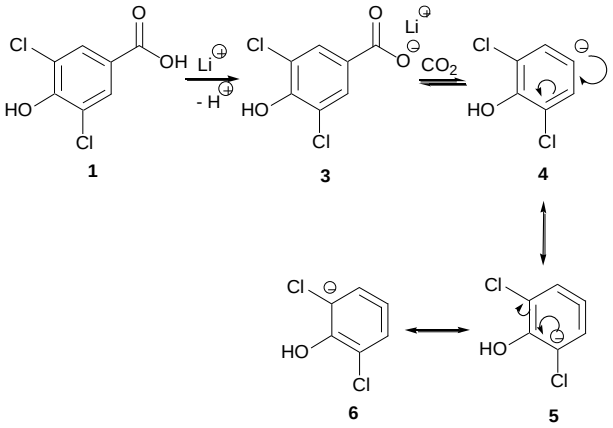
Compound **2** has molecular weight 335,9 g/mol with four chlor atom on its structure and this has been proved by EI-MS spectra. ^{1}H-NMR showed three types of protons of molecule **2** where each appeared at 3.80 ppm as CH_2 and at 7.20 ppm indicating four proton of aromatic ring. The carbon of –CH_2- appeared at 39.45 ppm. The methylene group, benzene ring and chlor atom in the molecule **2** are also confirmed by IR spectra.

When the reaction was monitored by TLC, it appeared as four spots. After isolation by flash column chromatography, only one spot can be collected (R_f = 0.74) and this was the main product of the reaction in 52 % yiled. The others were difficult to be isolated due to the small amount of each's.

According to the literatures, when carbonyl group reacts with $LiAlH_4$, it always changes to the corresponding alcohol. But in this case, it gave something different. A cross-linking product formed, like happened in the cross-linking of natrium benzoate which produced diphenylmethane. (Dabestani *et al*., 2005)

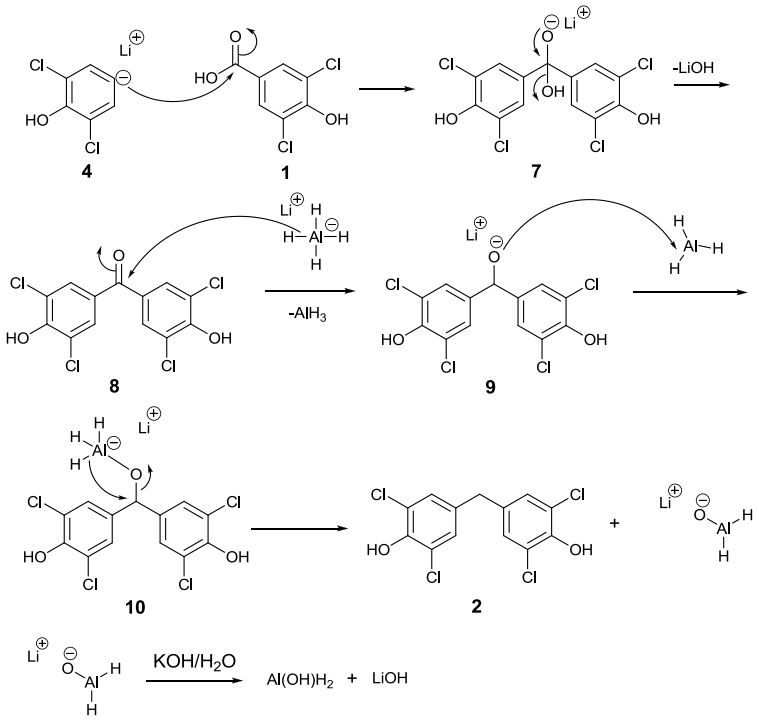
The proposed mechanism is illustrated in the scheme 2 below. First, the acid **1** formed a carbanion of 3,5-dichloro-4-hydroxybenzen-1-yde **4** through the decarboxylation of acid which stabilised resonance through the aromatic ring. Negative charge around C-3 **4** and C-5 **6** of carbanion is stabilised by negative induction of electron

withdrawing group of chlor atom. This is caused by the activation energy needed to decarboxylation on lithium salt is less than the decarboxylation process in the benzoic salt which does not have any electron withdrawing group.



Scheme 2. Decarboxylation of lithium salt **3** continued by stabilised resonance of carbanion 3,5-dichloro-4-hydroxybenzen-1-yde **4**

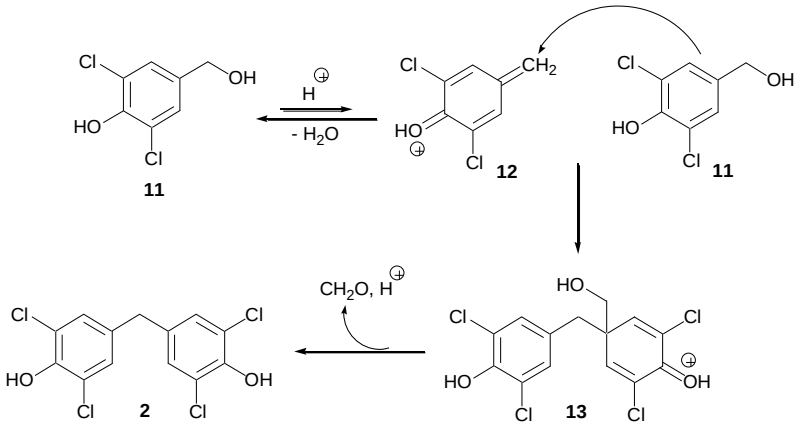
The carbanion **3** attacks the carbon atom of other carbon of carboxyl group **1**. This reaction goes through the electrophilic substitution reaction of aromatic ring which produce bis(3,5-dichloro-4-hydroxyphenyl)-hydroxy-methanolate ion **7**. This species then reacts eventually to form a keton by releasing the hydroxy group form **8** as bis(3,5-dichloro-4-hydroxyphenyl)methanone. The reduction process begins to form bis(3,5-dichloro-4-hydroxyphenyl)methanolate lithium salt **9** and furthermore reduced to **2**. (Scheme 3)



Scheme 3. Proposed mechanism of the synthesis of bis(3,5-dichloro-4-hydroxyphenyl)methane **2**

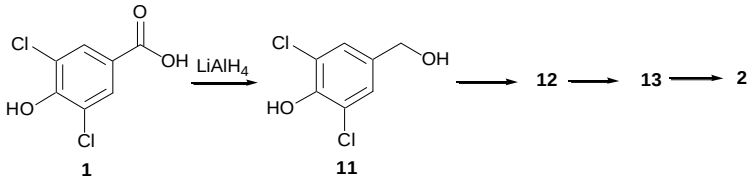
For the comparison, bis-phenol compound like bisphenol A (4,4′-Isopropylidenediphenol) which is known as BPA has a similar backbone to this bisphenol (bis(3,5-dichloro-4-hydroxyphenyl)methane **2)**. BPA can be synthesised from vaniline. Vaniline is converted to creosol (2-methoxy-4-methylphenol) and goes coupling through stoichiometric condensation with short-chain aldehydes by using Zinc acetate in two step reaction. (The Dow Company, 2012) The other example of the synthesis of BPA is the reaction between aldehyde or keton with phenol (5 mole equiv.) by using solid acid catalyst. This procedure has been used for the commercial synthesis of BPA. The process is done by using an acid catalyst to react acetone with phenol in a continuous, enclosed process under mild conditions of temperature and pressure. (Meylemans *et al*., 2012) Those both reactions have different mechanisms. When aldehyde or keton used, the coupling with phenol is easily but when carboxylic acid used, the coupling happened by involving the decarboxylation process.

These results are inline with the result that have been publihsed by Verhagen *et al*. (1998) although the reaction mechanism was proposed in different way. Bis(3,5-dichloro-4-hydroxyphenyl)methane **2** was formed by biosynthesis process from 3,5-dichloro-4-hydroxybenzylalcohol **11**. This process was under the influence of acids or metal salts present in the autoclaved sludge, heterolysis of 3,5-dichloro-4-hydroxybenzylalcohol **11** to higly stabilised benzylic carbocation **12** can take place. Attack of this electrophilic species on another molecule of 3,5-dichloro-4-hydroxybenzylalcohol **11** resulted in the formation of a dimer intermediate which then by losing the formaldehyde gave the bis(3,5-dichloro-4-hydroxyphenyl)methane **2**.



Scheme 4. Biosynthesis Formation of bis(3,5-dichloro-4-hydroxyphenyl)methane by Verhagen *et al*. (1998)

This reaction mechanism that proposed by Verhagen *et al*. can also be applied to the synthesis of this bis(3,5-dichloro-4-hydroxyphenyl)methane **2**. After the reduction of 3,5-dichloro-4-hydroxybenzoic acid **1** to 3,5-dichloro-4-hydroxybenzylalcohol **11**, like happened in usual reduction of acid, the alcohol formed **13** and ended by the formation of **2**.



Scheme 5. Proposed mechanism for the formation of bis(3,5-dichloro-4-hydroxyphenyl)methane **2** according to Verhagen *et al*. (1998)

3.2. Optimation of mole equivalent used of 3,5-dichloro-4-hydroxybenzoic acid and $LiAlH_4$ in the synthesis

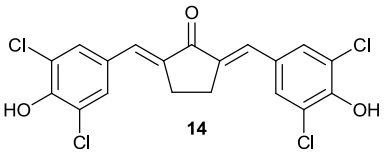
The best mole equivalent of the reaction between acid **1** and $LiAlH_4$ to produce **2** is when 1 : 4 of acid **1** and $LiAlH_4$ used. The results of these reactions can be read like in the table 1. The result showed that the higher the mol eq. of $LiAlH_4$ used, the higher the yield of **2** obtained. These results agree with the common theory of optimation, if one component is getting higher in a system, the product formed is normally getting higher too. And, in the reduction theory of carbonyl group by $LiAlH_4$, known each molecule of $LiAlH_4$ can reduce four carbonyl groups. It means that four carboxyl group reduced by one molecule of $LiAlH_4$ to aldehyde and then reduced more to its corresponding alcohol.

In this case, the alcohol from the carboxyl group was not obtained, but the product of acid cross-linking to the other acid molecule was formed. This cross-linking happened through the salt formation of acid which resulting from reaction with $LiAlH_4$ and which continued by the decarboxylation of salt. Then the reduction of keton continued to alcohol and the reduction of alcohol continued to alkane.

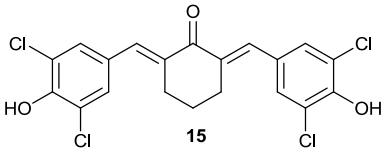
3.3. Prospect of the biological activity of (3,5-dichloro-4-hydroxyphenyl)methane **2**

The biological activity of bis(3,5-dichloro-4-hydroxyphenyl)methane **2** will be focused on its utility in medical and pharmaceutical use. From the Curcumin Research Center at Faculty of Pharmacy, Gadjah Mada University perspective, this bis(3,5-dichloro-4-hydroxyphenyl)methane **2** molecule has a similar structure to PGV-6 **14**, HGV-6 **15**, and GVT-6 **16** as mentioned above. On each aromatic ring of them have 3,5-dichloro-4-hydroxy group. PGV-6 **14**, HGV-6 **15**, and GVT-6 **16** possessed best activities as antibacterial agent in their analogs. These are being

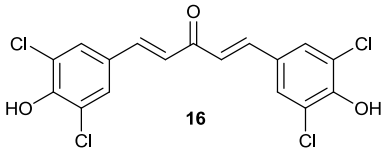
developed as antituberculosis agent. Due to this similarity, bis(3,5-dichloro-4-hydroxyphenyl)methane **2** could be developed as antibacterial agent, promisingly. Also this molecule could have the antifascioliasis activity due to its similarity to hexachlorophene and bithionil. (Melhorn and Armstrong, 2001)



PGV-6



HGV-6



GVT-6

Figure 1. Structure of PGV-6 **14**, HGV-6 **15** and GVT-6 **16**

4. Conclusion

The reaction of 3,5-dichloro-4-hydroxybenzoic acid **1** and $LiAlH_4$ did not give the corresponding alcohol, 3,5-dichloro-4-hydroxybenzyl alcohol through reduction reaction of the acid but gave an unexpected product which identified as bis(3,5-dichloro-4-hydroxyphenyl)methane **2**. This cross-linking product of the acid is the only product isolated and the alcohol was not obtained like theory said due to the cross-linking between those acids.

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