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Mechanism of Addition Reaction of Cyclohexanol on 17α-ethinylestradiol (EE2) with $FeCl_3$ Media

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Abstract

The addition reaction of cyclohexanol on 17α-ethinylestradiol (EE2) had been done by $FeCl_3$ media and the research of its reaction mechanism. The research steps had been done such as cross-coupling reaction. The separation used column chromatography, and the identification of compound used 1H-NMR spectroscopy technique, The interpretation of 1H-NMR spectrum indicated as an estradiol derivative, 17α(19-chlorovinilic-20 cyclohexane)estradiol. ***Keyword:*** Alkenyl halide, cross-coupling, 17α-ethinylestradiol

1. INTRODUCTION

This article is part of a previous published group research [1]. Alkenyl halides, are versatile substrates in various chemical transformations [2]. However, the availability of alkenyl halides is low and they are rare. As a result, the manufacture of such compounds is still challenging and very interesting for synthetic chemists. Alkynes are a class of compounds used for the synthesis of alkenyl halides, such as the addition of hydrogen halides and alkyl halides to alkynes. There are several reactions experienced by alkynes such as hydration reaction is an addition reaction by water (H_2O), addition reactions by Halogen Halides (HX), Hydrogenation reactions (H_2), and Halogen-Halogen addition reactions [3]. Mechanism of the alkyne addition reaction by the hydrogen halide can be seen in Figure 1.

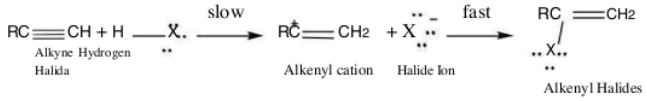

Figure 1. Alkyne Addition Mechanism by HX

Halides is a common structural motif in organic synthesis for the formation of C-C and C-N bonds in cross-coupling, transition-metal reactions, such as the Suzuki-Miyaura, Stille,

Sionogashira, and Buchwald-Hartwig reactions. [2]. Cross-coupling reaction is defined as a reaction that created a bond of C-C by way of merging two molecules with different structures [4]. Cross-coupling reaction is used for the formation of C-C bonds where this reaction is based on the

transmetalation of nucleophilic organometallic compounds with organic electrophiles, with the existence of transition metals as a catalyst [5]. Direct-coupling reactions using benzyl alcohol is still very

attractive because, their ability to leave by products into atoms efficient and environmentally friendly, namely H_2O [6]. Then the reaction is generally followed by a carbocation addition to the double bond and subsequent protonated [7]. The use of $FeCl_3$ has shown the catalytic activity of alcohols against various nucleophiles [8]. Alkyne used in the formation of an alkenyl halide is 17α-ethinylestradiol, where the compound is a drug commonly used in disease problems infertility, hormone hoarding, and osteoporosis [9]. Previous studies have shown that 17α-ethinylestradiol (EE2) is highly resistant to oxidation in the environment due to the presence of an ethinyl group at position 17, and because it has a high C≡C bond energy, 17α-ethinylestradiol (EE2) has an estrogenic ability 11-30 times stronger than estrogen (E2) [10]. Previous research involved alkynes and alcohols as the main reactants and HX as a source of halides and using the C-C coupling reaction. A compound formed from an addition of cyclohexanol at 17α-ethinylestradiol with anhydrous ferric chloride ($FeCl_3$) salt medium is an estradiol derivative compound with chloride alkenyl group is at atom C-17.

2. RESEARCH METHODS

Material. 17α-ethinylestradiol (Sigma aldrich) 98% purity, cyclohexane, anhydrous iron (III) chloride, dichloromethane pa, n-Hexane, chloroform pa, ethinyl acetate, aquadest, methanol, H_2SO_4, TLC plate F_{254}, silica gel 60 (70- 230 mesh), aluminum foil, cotton.

The equipment used was Beaker, spatula, measuring pipette, eppendorf micro pipette, dropper, stative, clamp, measuring cup, watch glass, capillary tube, vial, tweezers, spray bottle, TLC elution chamber, gravity chromatography column, analytical balance, fume hood, oven mert, rotary shaker, centrifuge tube.

Cross-Coupling Reaction

Anhydrous iron (III) chloride (16 mg, 0.1 mmol), cyclohexane (221 mg, 1.2 mmol), and dichloromethane solvent (3 mL) were mixed in a centrifuge tube by shaking. After being shaken for several minutes, the mixture was then added with 17α-ethinylestradiol (132 mg, 1 mmol) and continued shaking for 48 hours. During the process, the reaction was monitored by testing thin layer chromatography.

Separation of compound

After the reaction was completed, the reaction mixture was separated by gravity column chromatography using n-hexane:ethinyl acetate as mobile phase with several ratios of 10:0; 9:1; 8.5:1.5; 8:2; 7:3.

Identification of Sample Fraction

The fraction result from the separation was further identified using the 1H-NMR (Nuclear Magnetic Resonance) testing technique.

3. RESULT AND DISCUSSION

Cyclohexanol Addition Reaction Stage in EE2 with $FeCl_3$.

The results of the reaction were carried out in the first step, namely the process of mixing the reaction between $FeCl_3$, cyclohexanol, and dichloromethane into a centrifuge tube and shaken using a Rotary Shaker for 30 minutes. This conditioning process is carried out with the aim of forming a $FeCl_3$-cyclohexanol complex, which causes the formation of a dimeric ether compound. After that, EE2 is added and can then immediately attack the dimeric $FeCl_3$-ether complex, where the triple bond acts nucleophilic. At this stage, monitoring was carried out using thin layer chromatography (TLC). TLC analysis is an analysis of chemical components using the principle of absorbent and partition, where the chemical components will move following the mobile phase this is because the absorbent absorption of chemical components is not the same so that these components will move with different

distances [11]. The reaction was stopped when it was seen that there were other components separated from the standard (there were other stains with different Rf from the standard) the Rf value of the TLC test results can be seen in Table 1.

Table 1. Rf value of TLC results from the reaction mixture

	Rf		
	EE2	S	X
$CHCl_3$ (9.5) : EtOAc (0.5)	0.3	0.5	0.5
$CHCl_3$ (9) : n-hexane (1)	0.3	0.31	0.31
n-hexane (7): EtOAc (3)	0.57	0.67	0.67

Description: S = Spike (Standard + sample)
X = sample

Separation of the Addition Reaction Mixture

Gravity column chromatography technique was performed with a column length of 30 cm and a diameter of 1.5 cm. ±15 g of silica gel was used, then soaked for 1x24 hours using 100 ml of n-hexane as solvent. The eluent used for steroid and tripenoid compounds consisted of n-hexane and ethyl acetate in a ratio of 16:4; 17:3; and 18:2, where the n-hexane solution is a non-polar solvent and ethyl acetate is a semi-polar solvent [12]. In this research, TLC analysis was carried out on several solvents, then the eluent for column chromatography was obtained, namely n-Hexane:Ethylacetate with several ratios, namely 20:0; 36:4; 34:6; 32:8; 14:6. The sample will be eluted based on the interaction with the stationary phase and the flow reaction rate with a time range of 6-14 seconds/drop, then it is accommodated into 60 vials and each vial holds 2 ml/vial. Furthermore, the eluate was grouped using hexane/ethyl acetate eluent (8:2). The Rf value of the TLC analysis on the separation of the reaction mixture before grouping can be seen in Table 2.

Table 2. Rf value of TLC analysis on eluate at intervals of 3 vials using n-hexane (8) : ethyl acetate (2) eluent.

No. Vial	Rf value	No. Vial	Rf value
03		36	0.5
06	0.94	39	-
09	0.94	42	0.22
12	0.94	45	0.22
18		48	0.22
21		51	0.22
24	0.5	54	0.22
27	0.44	57	0.22
30	0.52	60	-
33	0.48	EE2	0.22

From the existing Rf data, 3 groups of fractions were obtained, namely I (1-22); II (23-36); III (37-60) and fraction II were carried out in a further step, 1H-NMR test because fraction II showed a different stain appearance with the characteristics of the standard stain (EE2) and had a higher Rf value than the standard Rf.

Structure Determination

Fraction II was analyzed using a Nuclear Magnetic Resonance Proton (1H-NMR) instrument to determine the structure of the compound, using Chloroform-D ($CDCl_3$) solvent and measured at a frequency of 500 MHz. Table 3 shows the spectroscopic data for 1H-NMR fraction II by comparing the standard EE2 1H-NMR data and the comparison journal.

Table 3. Data tabulation of 1H-NMR fraction II with standards and comparison journals.

Proton position	EE2* δ H	Standard EE2 δ H	Fraction I δ H
1	7,05	7,088	7,517
2	6,50	6,569	7,509
4	6,43	7,945	7,450
6α	2,7[a]	2,722	2,349
6β	2,7[b]	2,718	2,335
7α	1,25	1,280	1,269
7β	1,76	1,718	1,670
8	1,30	1,375	1,269
9	2,04	2,025	2,000
11α	2,28	2,299	2,281
11β	1,30	1,389	1,319
12α	1,76	1,712	1,605
12β	1,65	1,692	1,670
14	1,31	1,399	1,239
15α	1,65	1,692	1,670
15β	1,31	1,399	1,239
16α	2,10	2,182	2,272
16β	1,86	1,858	1,319
18	0,75	0,857 *s*	0.814
20	3,31	3,297 *d* (*J* = 5 Hz)	5,350
OH	5,29	4.334 *s*	4,137 4,116

Exp*= comparison journals.

In steroids, ring alternation plays an important role. Chemical shift H 1.57 ppm; H 1.66 ppm ; H 2.33 ppm is predicted to be a proton signal contained in the cyclohexanol group [14]. The following interpretation of the chemical shift tabulation data in fraction II is as follows:

- The chemical shift of H 4.116 ppm indicates the presence of –OH group attached to the C-17 group.
- The chemical shift of H 4.137 ppm indicates the presence of an –OH group attached to the C-3 group.
- The aromatic proton signal appears at the H shift of 7.517; 7.509; 7,450 ppm
- The signal of the proton bound to the C-8 methyl is in the H shift of 0.814
- A shift of 5.350 identifies the presence of a proton attached to a double bond

(C-20).

The shift for the alkenyl group shifted in the range of 4.4-7.5 ppm [15]. The signal for C-20 in fraction II shows a shift at H 5,350. This indicates that there are no more alkyne groups at C-20. From the tabulated data, a new compound derived from estradiol was obtained and the structure and name of the compound were obtained as shown in Figure 2.

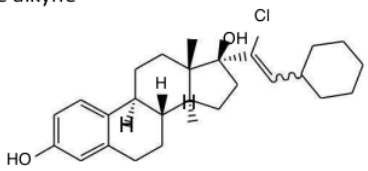

Figure 2. 17α(19-chlorovinilic-20 cyclohexane)estradiol.

Addition Reaction Mechanism

$FeCl_3$ here acts as a strong Lewis acid and with this property, the oxygen atom is partially positively charged due to the attraction of the electron pair present in Iron(III). The oxygen atom in cyclohexanol is unstable because it binds to $FeCl_3$, then the oxygen atom affects the carbon-oxygen bond in the cyclohexyl ring to stabilize its partial charge. The proton that binds to oxygen is then released by means of the released hydroxyl anion which binds it to form a water molecule (H_2O) and a dimeric ether compound. In the presence of a nucleophile, the ether is re-polarized by $FeCl_3$, resulting in a new benzylic carbocation and an iron (III) atom in $FeCl_3$ which has a partial negative charge then EE2 is added which in this case is nucleophilic. The ethinyl group which has an electron pair attacks the cyclohexyl carbon to form a vinylic carbocation and an iron complex. This vinyl carbocation then stabilizes itself by binding to one of the chlorines present in $FeCl_3$. The mechanism of the addition reaction is shown in figure 4

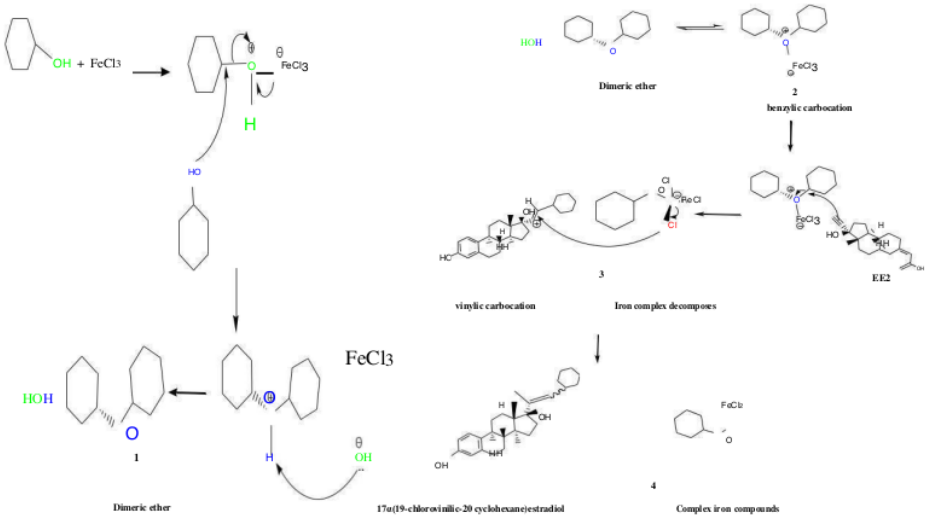

Figure 4. Proposed Reaction Mechanism.

4. CONCLUSION

1. The addition reaction between 17α-ethinylestradiol and cyclohexanol with $FeCl_3$ media produces a 17α(19-chlorovinilic-20 cyclohexane)estradiol, where the alkyne group is converted to an alkenyl halide group. This is evidenced by a chemical shift in the proton C-20 which is 5.350 ppm.
2. The mechanism of formation of alkenyl halides by addition reaction begins with the formation of dimeric ether from cyclohexanol using $FeCl_3$ as a catalyst and produces an environmentally friendly by-product in the form of water (H_2O).

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