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Research Article

Formation Reaction of 17α (chlorovinyl-3-methyl-butene) estradiol Through the Addition Reaction of a Terminal Alkyne to Ethinylestradiol With a $ZnCl_2$ Catalyst

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Abstract: The addition reaction had been done on the terminal alkynes of 17α-ethynylestradiol with $ZnCl_2$ and HCl catalyst mediated by dichloromethane. The reaction conditions were carried out at a temperature of 70°C for 29 h, the separation of the reaction properties was carried out using Gravity Column Chromatography, and the reaction products were identification using by Nuclear Magnetic Resonance (NMR). The catalyst used was a cationic ligand coordinate, where Zn acts as the central ion and 2-propanol as the ligand. In the reaction mechanism, the reaction begins with the formation of dimeric ether. $ZnCl_3$ catalyst acts as Lewis acid which converts alcohol to dimeric ether and forms a complex with $ZnCl_3$. The nucleophilic terminal alkyne then attacks the C-O bond of the ether to form a vinyl carbocation which then attracts a chlorine atom from $ZnCl_3$ which was complex bound with ether, resulting in a reaction product of 17α(chlorovinyl-3-methyl-butene)estradiol.

Keywords: Alkenyl Halide, Addition Reactions, 2-Propanol, 17α-ethinylestradiol, Catalyst $ZnCl_2$

Introduction

An addition reaction is a reaction in which a double bonded (unsaturated) hydrocarbon compound is converted into a single (saturated) hydrocarbon compound by adding atoms from another compound[1]. Addition to the terminal alkyne will produce products that follow the Markonikov rule such as alkenyl halides[2]. Figure 1 shows the general reaction for the synthesis of alkenyl halides at terminal alkynes[3].

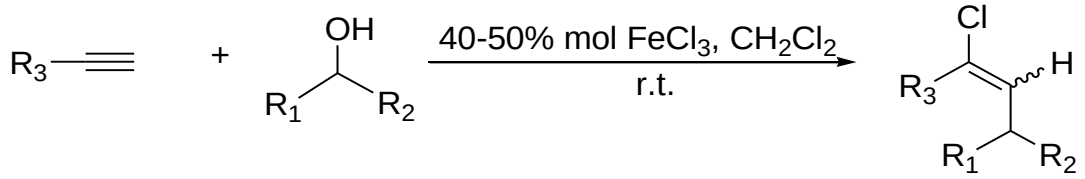

Image 1. The general reaction for the synthesis of alkenyl halides[3].

Alkenyl halides are required in synthesis because they are the starting compounds in several cross-coupling synthesis methods (forming carbon-carbon bonds)[4]. However, the availability of

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alkenyl halides is very small and tends to be expensive[3], thus new methods for the synthesis of alkenyl halides began to be sought. One method for synthesizing alkenyl halides by directly reacting alkynes and alcohols is carried out in the presence of stoichiometric amounts of strong bases such as n-BuLi or boron trichloride (BCl_3). However, this method requires a long reaction time, has high toxicity and the chemicals used are relatively expensive[5]. In general, alkenyl halides are prepared from ketones or aldehydes using halogenating agents, such as phosphorus penthalide, acetyl halide and POX3 by prolonged heating in a solvent with a high boiling point[6].

Alkenyl halide synthesis method in the research of "New and Efficient Iron Halide Mediated Synthesis of Alkenyl Halides through Coupling of Alkynes and Alcohols"[3], shows that Anhydrous $FeCl_3$ acts as a reaction medium, where $FeCl_3$ acts as an electron donor for halide elements. In this study using terminal alkynes, namely monosubstituted alkynes and alcohols used alcohols bound to aromatic rings, where the alcohols are all secondary alcohols. However, the addition method of the terminal alkyne bonded by sp^3 carbon to the 17α-ethinylestradiol substrate with secondary alcohol using $ZnCl_2$ and HCl catalyst has not been carried out.

Reaction development using zinc chloride ($ZnCl_2$) catalyst with hydrogen chloride (HCl) has been widely developed in organic synthesis, like addition method with alkyne, HCl and $ZnCl_2$ catalyst in a ratio of 10:10:3[7] and also alkynes were reacted with HCl and $ZnCl_2$ catalyst in dichloromethane and the reaction products were also investigated with respect to their stereochemistry[8]. The purpose of this research is to test the reaction and identify and determine the structure of the product compound to see the changes that occur in the reaction. This research is a continuation of our group's research[9].

Materials and Methods

Materials

4-digit RADWAG analytical balance, reflux kit, two neck flask, thermometer, micro Eppendorf pipette (5-1000 μL), tweezers, measuring cup, spatula, stirring rod, dropping pipette, beaker, capillary tube, cutter, chamber, memmert oven, ESCO fume hood, vials, glass spray bottles, gravity column chromatography (1.5 x 15 cm), and Nuclear Magnetic Resonance (NMR) spectroscopy.

The ingredients used in this research are 17α-ethinylestradiol purity ≥ 98% (Sigma Aldrich), $ZnCl_2$, 2-propanol, HCl pa, dichloromethane pa, methanol pa, ethanol pa, n-hexane pa, chloroform pa, TLC plate F254, silica gel 60 (70-230 mesh ASTM), 10% sulfuric acid in methanol, and aluminum foil.

Methods

Addition reaction

The action step of the addition reaction was carried out by reacting 46 mg $ZnCl_2$ 0.337 mmol (2 eq) with 5 mL dichloromethane, 200 μL 5 mmol HCl (29.64 eq), and 125 μL 3.373 mmol 2-propanol (20 eq) in the following way: heated. Then 17α-ethinylestradiol 50 mg 0.167 mmol (1 eq) was added. The mixture was heated in a water bath at 70°C and the reaction process was controlled using the TLC method with chloroform and n-hexane as eluents. The reaction was stopped until the EE2 standard and the catalyst had finished reacting and when observed, stains of components other than the EE2 standard were seen on the TLC plate. After the reaction was stopped, the reaction mixture was cooled to room temperature and the solvent was evaporated in a fume cupboard.

Separation of addition reaction mixtures

After the reaction was completed, the reaction mixture was separated by means of gravity column chromatography (KKG) using the mobile phase $CHCl_3$: n-hexane (6 : 4) weight v/v. The results of the separation (eluate) were then collected into vials with a volume of 1 mL/vial. The eluate obtained was then analyzed by TLC test and grouped based on the appearance of the stain and then evaporated in a fume hood to obtain 1 mg of 17-α(chlorovinyl-3-methyl-butene) estradiol reaction product.

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Determination of the addition product structure of 17α-ethinylestradiol

The fractions obtained containing pure compounds were then identified using Nuclear Magnetic Resonance (NMR) to determine the structure of the resulting compound.

Results And Discussions

Addition Reaction of Alkyne Ethinylestradiol With $ZnCl_2$ Catalyst

The reaction was initiated by preparing a mixture of catalysts $ZnCl_2$ and HCl with the reactant, namely 2-propanol, then dichloromethane solvent was added. The mixture was heated for 15 min and then 17α-ethinylestradiol (EE2) was added to it. The reaction mixture was heated for 29 h at 70°C. The reaction was initiated by the addition of the ZnC_2 and HCl catalysts which functioned to initiate the formation of a complex between the catalyst and the reactant, namely 2-propanol.

During the heating process, it causes evaporation of the solvent so that the solvent is periodically added and the total amount of solvent (dichloromethane) added is 40 mL. Reaction Mixture and standards 17α-ethinylestradiol analyzed on F_{254} thin layer chromatography (TLC) plates using the eluent composition of ethyl acetate and n-hexane. The reaction was controlled by TLC for the first time after 1 h of heating, then controlled again after 3 h, 6 h, 9 h, 12 h, 15 h, 18 h, 21 h, 24 h, 27 h-and 29 h. The reaction is stopped when the observed standard or reagent has finished reacting. The reaction can be seen to have completely reacted because of the reactant that acts as the limiting reagent. The reaction was stopped at 29 h because it was observed that a new product had formed, and it was observed that the reaction had completely reacted. From the standard TLC and the reagent it has been observed that the limiting reagent is $ZnCl_2$. The presence of a limiting reagent in this reaction causes the reaction to begin to saturate and no further reaction changes occur.

Separation of the Reaction Mixture

Separation of the reaction mixture was carried out using the Gravity Column Chromatography (KKG) technique with a column length of 15 cm and a diameter of 1.5 cm. The separation phase begins by determining the mobile phase first. The composition of the mobile phase (eluent) used was determined by TLC analysis. Several TLC analyzes were reported for determination of eluent composition in the analysis17α-ethinylestradiol namely cyclohexanol:ethylacetate:chloroform (1:1:1)[10], and hexane:chloroform:methanol (1:3:0,2) and ethyl acetate:chloroform (2:8)[11]. TLC analysis was carried out on the materials mentioned above, until a suitable eluent was obtained, namely $CHCl_3$: n-hexan (6:4).

This column chromatography uses a normal phase column, where the stationary phase is polar, namely silica gel 60 (70-230 mesh ASTM), while the mobile phase is non-polar after obtaining a suitable mobile phase, namely $CHCl_3$:n-hexane (6:4), then 5 g of silica gel was weighed and soaked for 1 h with the eluent to be used, namely $CHCl_3$:n-hexane (6:4).

As in the analysis using TLC, the sample will eluted based on its interaction with silica gel as the stationary phase, compounds that have the same polarity level as silica gel will be retained in the column for a long time, while non-polar and semi-polar compounds will move faster out of the column, with flow rate of 2 seconds per drop and accommodated in 100 vials, with a volume of 2 mL per vial. The elution results can be referred to as eluate. The eluate contained in these 100 vials will each be analyzed by TLC using the same eluent as KKG to see the Rf value of the eluate in each vial. TLC analysis of eluate was performed with a range of five vials and EE2 as standard. Samples that have the same Rf value are combined to get 5 fractions, namely F1 (vials 1-17); F2 (vial 18); F3 (vial 19); F4 (vials 20-25); F5 (vial 26-100) then the F3 fraction was determined as a product of the reaction.

F3 Fraction Identification Stage

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The F3 fraction was analyzed using Nuclear Magnetic Resonance (1H-NMR) and Nuclear Magnetic Resonance Carbon (^{13}C-NMR) instruments to determine its structure. Tabulation of chemical shifts is shown in Table 1 and Table 2. In Table 1, the F3 fraction was analyzed using ^{1}H-NMR by dissolving it in chloroform-D ($CDCl_3$) solvent and measured at a frequency of 500 MHz.

In table 1, a typical proton signal is shown in the steroid nucleus which has an angular methyl proton signal at δH 0.717 ppm[12]. For the protonation signal on aromatic C-1 (H-1) it is at a shift of δ 7.04 ppm; H-2 at δ 6.49 ppm; H-4 at δ 6.43 ppm; as well as for C-18 for methyl at δ 0.74 ppm[13].
The interpretation of the chemical shift tabulation data for the F3 fraction is as follows:
The chemical shift of δ 5.613 ppm indicates the –OH group attached to the C-3 group. The chemical shift of δ 1.524 ppm indicated the presence of –OH groups attached to the C-17 group. Aromatic proton signal appears at δ 7.044 ppm; δ 6.666 ppm; δ 6.544 ppm. The proton signal bound to C-18 methyl is at a shift of δ 0.717 ppm. The proton signal at δ shift of 7.027 ppm shows the proton attached to the double bond (C-20). Proton signal at shift δ 6.683 ppm with multiplet multiplicity shows protons on H-21. Proton signals bound to C-22 and C-23 methyl are at a shift of δ 0.882 and δ 0.872 ppm.

Proton signal bound to H-20 on standard 17α-ethinylestradiol showed a terminal alkyne group at δ 2.598, but the F3 fraction no longer showed this shift. The signal for the H-20 F3 fraction showed a chemical shift at δ 7.044 ppm, this indicated that there was no terminal alkyne group at C-20, but had changed to an alkenyl compound group. The shifts for alkenyls range from about 4.4 to 7.5 ppm[15].

Table 1. Tabulation of the ^{1}H-NMR spectrum of the F3 fraction with standard 17α-ethinylestradiol (EE2) and comparative journal values[14].

Proton Potition	**17α-ethinylestradiol [14]**	**Standar 17α-ethinylestradiol δ H**	**F3 Fraction (*m* ; J = Hz) δ H**
1	7.05	7.144	6.683 (*d* ; 8.5 Hz)
2	6.50	6.609	6.666 (*d* ; 8.5 Hz)
4	6.43	6.551	6.544 (*s*)
6α	2.7[a]	2.829	2.703 (*m*)
6β	2.7[b]	2.806	2.703(*m*)
7 α	1.25	1.326	2.601(*m*)
7β	1.76	1.704	1.867(*m*)
8	1.30	1.430	1.410 (*m*)
9	2.04	2.010	2.777(*m*)
11α	2.28	2.226	2.250(*m*)
11β	1.30	1.382	1.695(*m*)
12α	1.76	1.862	1.665(*t*)
12β	1.65	1.791	1658(*m*)
14	1.31	1.393	1.391(*m*)
15α	1.65	1.695	1.658(*m*)
15β	1.31	1.389	1.357(*m*)
16α	2.10	2.173	2.064(*t*)
16β	1.86	1.862	1.851 (*t*)
18	0.75	0.871 (*s*)	0.717 (*s*)
20	3.31	2.598	7.044 (*d*)
21	-	-	2.526 (*m*)
22	-	-	0.882 (*d* ;5 Hz)
23	-	-	0.872 (*d* ;5 Hz)
OH	5.29	1.949	1.524 (*s*)
OH	5.29	4.713	5.613 (*s*)

Furthermore, in table 2, the F3 fraction was analyzed using Nuclear Magnetic Resonance Carbon (13C-NMR) dissolved in chloroform-D ($CDCl_3$) and measured at a frequency of 125 MHz.

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Benzene carbons adsorb in the δ 128.5 ppm range, either as a pure liquid or as a solution in $CDCl_3$ or CCl_4[14]. Interpretation of the chemical shift data tabulation of sample F3 in table 2 shows a chemical shift of δ 152.927 ppm which is an aromatic carbon that binds the –OH group, namely C-3. The chemical shift δ 78.221 ppm indicated the presence of a –OH group attached to C-17. The aromatic carbon signal appears at the C-1 chemical shift δ 126.934 ppm; C-2δ 112.9201 ppm; C-4 δ 152.927 ppm; C-5 δ 140.948 ppm; and at C-10 it is at δ 130.841 ppm. The carbon signal bound to C-18 methyl is at a shift of δ 14.226 ppm. The carbon signal at δ 127.481 ppm shift indicates the carbon attached to the double bond, namely at C-20. The carbon signal at the δ shift of 140.948 ppm indicates the carbon double bond that binds –Cl, namely at C-19. Carbon signal at δ 152.927 ppm shift indicates C-21. Carbon signal at δ 21 shift.

The signal of the carbon bonded to C-20 on the EE2 standard shows the terminal alkyne group which is at δ 74.199 ppm, but in the F3 fraction it no longer shows this shift because the signal for the carbon bonded to C-20 for the F3 fraction showed a shift at δ 127.481 ppm indicating that the terminal alkyne had changed to an alkenyl compound. The formation of alkenyl halide compounds is supported by a chemical shift at δ 140.948 ppm, namely C-19 where there is a double carbon that binds –Cl.

Table 2. Tabulation of the ^{13}C-NMR spectrum of the F3 fraction with 17α-ethinylestradiol (EE2) standard and comparative journal[14].

Carbon Potition	17α-ethinylestradiol [14]	Standar 17α-ethinylestradiol δ C	F3 Fraction δ C
1	126.0	126.648	126.934
2	112.7	112.757	112.901
3	154.9	153.378	152.927
4	114.9	115.320	115.406
5	137.1	138.366	140.948
6	29.1	29.718	30.265
7	27.4	27.261	26.282
8	39.9	39.451	39.759
9	43.3	43.579	41.611
10	130.0	132.693	127.481
11	26.9	26.474	28.039
12	32.5	32.790	29.670
13	46.6	47.207	42.063
14	48.9	49.501	41.611
15	22.4	22.884	21.128
16	38.5	39.019	32.022
17	78.1	80.016	78.221
18	12.7	12.786	20.811
19	88.9	87.541	140.948
20	74.9	74.199	127.481
21	-	-	22.798
CH_3-22	-	-	21.396
CH_3-23	-	-	21.396

Based on the above interpretation, it can be assumed that the product of the reaction is 17α(chlorovinyl-3-methyl-butene)estradiol (Figure 2).

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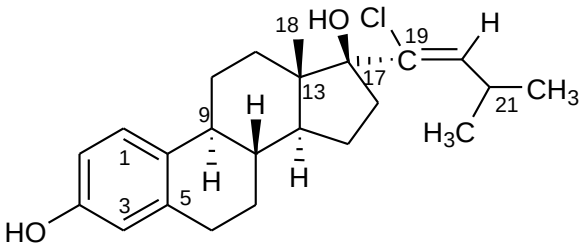

Figure 2. Structure of 17α(chlorovinyl-3-methyl-butene)estradiol.

Conclusion

1. The mechanism of the addition reaction for the formation of alkenyl halides begins with the formation of a dimeric ether from the joining of two secondary alcohols, namely 2-propanol using a $ZnCl_2$ and HCl catalyst as a medium for the formation of alkenyl halides and produces an environmentally friendly byproduct in the form of H_2O.
2. The compound resulting from the addition is 17α(chlorovinyl-3-methyl-butene)estradiol.

References

[1] E.V. Anslyn, D.A. Dougherty.Modern Physical Organic Chemistry. University science books; 2006.
[2] T.W.G. Solomons, C.B. Fryhle , S.A. Snyder. Organic Chemistry. 12ed. John Wiley & Sons, Inc.; 2016.
[3] S. Biswas, S. Maiti, U. Jana. New and Efficient Iron Halide Mediated Synthesis of Alkenyl Halides through Coupling of Alkynes and Alcohols. Eur. J. Org. Chem., (14) (2009) 2354-2359. doi:10.1002/ejoc.200900104
[4] S.R. Chemler, D. Trauner, S.J. Danishefsky. The B-Alkyl Suzuki–Miyaura Cross-Coupling Reaction: Development, Mechanistic Study, and Applications in Natural Product Synthesis. Angew. Chem .Int. Ed., 40(24) (2001) 4544-4568.
[5] G.W. Kabalka,M.L. Yao, S. Borella, Z. Wu. Alkenylation of allylic alcohols using alkenylboron dihalides: a formal transition-metal free Suzuki reaction. Chem Commun., (19) (2005) 2492-2494.
[6] Y.R. Yang, Q. Zhang, F.T. Du, J.X. Ji. Fe powder catalyzed highly efficient synthesis of alkenyl halides via direct coupling of alcohols and alkynes with aqueous HX as exogenous halide sources. Tetrahedron, 71(25) (2015) 4304-4311.
[7] R. Maroni, G. Melloni, G. Modena. The stereochemistry of the electrophilic additions to triple bonds via linear vinyl cations. J. Chem. Soc. Chem. Commun., (15) (1972) 857-858.
[8] M. Hanack, E. Weber. Vinylkationen, 39. Zinkchlorid-katalysierte Chlorwasserstoff-Additionen an Cyclopropylalkine. Chem Ber., 116(2) (1983) 777-797.
[9] E.J. Pongoh, R.J. Rumampuk, N.S. Dwiyanti. Mechanism of Addition Reaction of Cyclohexanol on 17α-ethinylestradiol (EE2) with $FeCl_3$ Media. NeuroQuantology, 20(19) (2022) 603-608
[10] S.A. Bhawani, O. Sulaiman, R. Hashim, M.N. Mohamad Ibrahim. Thin-layer chromatographic analysis of steroids: A review. Trop. J. Pharm. Res., 9(3) (2010) 301-313. doi:10.4314/tjpr.v9i3.56293
[11] A.R. Fakhari, A.R. Khorrami, M. Shamsipur. Stability-indicating high-performance thin-layer chromatographic determination of levonorgestrel and ethinyloestradiol in bulk drugs and in low-dosage oral contraceptives. Anal. Chim. Acta., 572(2) (2006) 237-242. doi:10.1016/j.aca.2006.05.029
[12] R. Rumampuk. Elucidation of saponin structures from seeds of Barringtonia asiatica (L.) Kurz. Padjadjaran University, Bandung.
[13] A. Lommen, R. Schilt, J. Weseman, A.H. Roos, J.W.V. Velde. Application of 1D 1 HNMR for fast non-targeted screening and compositional analysis of steroid cocktails and veterinary drug formulations administered to livestock. J. Pharm. Biomed. Anal., 28 (2002) 87-96.

E-ISSN: 2720-9326
P-ISSN: 2716-0459
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[14] J.A. Franca, A. Navarro-Vázquez, X. Lei, H. Sun, C. Griesinger, F. Hallwass. Complete NMR assignment and conformational analysis of 17-α-ethinylestradiol by using RDCs obtained in grafted graphene oxide. Magn. Reson. Chem., 55(4) (2017)297-303.
[15] M.R. Silverstein, F.X. Webster. Spectrometric Identification of Organic Compounds. Wiley & Sons, Inc.; 1981.