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Review

Claisen Rearrangement Toward Cyclic Compound on Different Organic Synthesis Methods: Short Review

Rizki Rachmad Saputra, Reny Rosalina*, Dimas Pramudita, Oktavia Rahmi Wulandari, Yuneta, Amanda Natania Gracia, Tina Sugiyani, Marsya Imelya

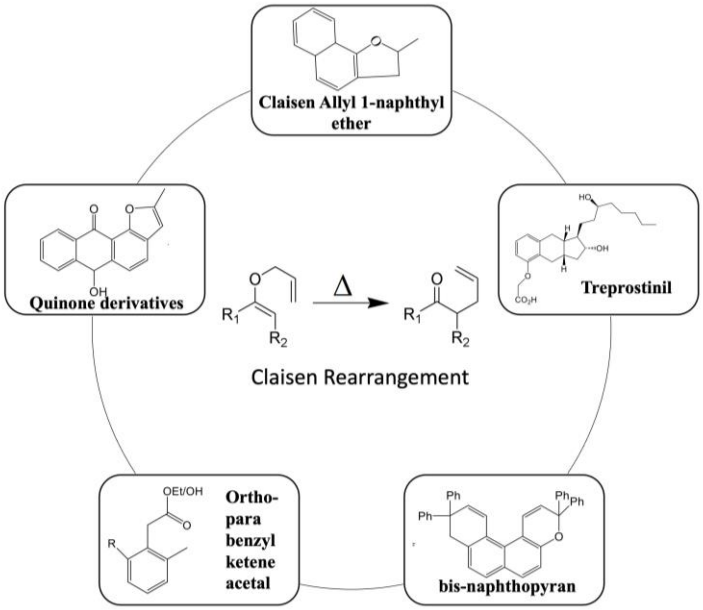
[1]Department of Chemistry, Faculty of Mathematics and Science, Universitas Palangka Raya, Palangka Raya 73112, Central Kalimantan, Indonesia

Abstract

The synthesis of functional and complex organic compounds is majorly performed by the Claisen rearrangement method. Claisen rearrangement is one of [3,3] sigmatropic rearrangements, a complex method in the synthesis of organic compounds, where it is mostly used to construct stereoselective compounds. It can be combined with other synthesis methods to synthesize organic compounds giving satisfactory results based on the method used, temperature, time, and yield produced. This review aimed to summarize several recent advances in synthesizing organic compounds through Claisen rearrangement reactions. An understanding of the mechanism and applications of this reaction might improve the ability to synthesize innovative and useful organic compounds in various fields of life sciences.

Keywords: *cyclic compound synthesis, rearrangement reactions, Claisen Rearrangement, reaction mechanism*

Graphical Abstract



* Corresponding author
Email addresses: renyrosalina@mipa.upr.ac.id

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Introduction

The sigmatropic reaction is one of the pericyclic reactions that can rearrange a molecule with a cyclic geometry [1]. The word sigmatropic comes from the Greek troops which means “turn”. Sigmatropic rearrangement is an intramolecular pericyclic reaction, where the σ in the reactants are broken so that the π bonds can be reorganized to form new σ bonds in the product [2,3]. The sigmatropic rearrangement results in the same or constant number of π bonds or a constant number of bonds in the reactants and products [4,5]. The stereochemistry of the sigmatropic rearrangement is determined by the symmetry of the orbitals involved in the reaction. Orbitals on the σ bond that are broken and the orbitals ρ on the π bond are the new σ in the product [6]. There are two patterns resulting from sigmatropic rearrangement, suprafacial rearrangement, and interfacial rearrangement. The suprafacial rearrangement involves 6 or fewer atoms and produces a new σ bond on the same side of the π bond. Whereas the interfacial rearrangement produces a new σ bond on the opposite side of the π bond [7].

Claisen rearrangement is one of the types of [3,3]- sigmatropic rearrangement methods used in the stereoselective construction of organic synthesis. A chemist named Rainer Ludwig Claisen proposed a rearrangement reaction between two different carboxylic esters or between esters and ketones in the presence of a base [8]. This reaction allows the replacement of alkoxide groups with different alkyl or aryl groups thus paving the way for various structural modifications that can improve the properties and activity of organic compounds. Claisen rearrangement is an important reaction in the synthesis of highly functional organic compounds and complex natural products [9].

The Claisen rearrangement mechanism involves the arrangements of compounds containing alkoxide and carbonyl groups, resulting in the formation of compounds with new, more stable carbon bonds. The reactants for this reaction are ester compounds or ketone compounds. Subsequently, the reaction process is conducted in a basic atmosphere to facilitate the removal of the alkoxide group [10]. The Claisen rearrangement is carried out at a temperature higher than of 220°C [11].

Claisen rearrangement is widely applied in organic synthesis and can be combined with other synthesis methods. The combination of Claisen rearrangement with other methods such as metathesis in synthesis can be carried out in various functional molecules so that the combination of these methods can be a strategy to be utilized in the design of various molecules suitable for the fields of medicinal chemistry and materials science [12]. One the types of Claisen rearrangements is the Aza-Claisen rearrangement (ACR). ACR is used as a key in the synthesis of complex alkaloids and is now a frequently emerging field in synthetic organic chemistry experiments [13]. A unique application of ACR is the ring expansion induced by ACR which can guarantee stereochemical results superior to [3,3]-sigmatropic rearrangements [14]. As for the recent developments in ACR already adding more options for ring expansion to the synthetic chemist's toolbox [15].

In the research and development of organic compounds, Claisen rearrangement continues to be used and applied to create new compounds with complex and more stable structures, so a literature study is needed regarding the synthesis of organic compounds with the Claisen rearrangement mechanism. This literature study aims to analyze recent advances in synthesizing organic compounds through Claisen rearrangement reactions. The review was carried out using the literature study from national and international reputable journal articles within the last 10 years. A better understanding of the mechanism and applications of this reaction can improve the ability to synthesize innovative and useful organic compounds in various fields of life sciences.

The claisen rearrangement reaction in organic compounds synthesis

There has been a lot of research on organic synthesis using Claisen rearrangement. There are a variety of synthesized compounds that use Claisen rearrangement to obtain complex synthesis results. The following is a list of organic

synthesis research using Claisen rearrangement that has been done.

The Claisen Rearrangement Reaction of Allyl 1-naphthyl ether

Based on research conducted by Pramesti & Okada [16] Claisen rearrangement reaction on the synthesized compound allyl 1-naphthyl ether was successfully carried out with low reaction temperature and short time using Microwave Assisted Organic Synthesis (MAOS) method with $FeCl_3$ catalyst. In this study, the synthesis of allyl 1-naphthyl ether was carried out through the substitution reaction of allyl groups on 1–naphthol compounds by heating for 8 hours at 58°C. Furthermore, the synthesized product was identified by HPLC to determine its purity and analyzed its structure using the ^{1}H–NMR method. This research was conducted using a variety of solvents including 1,2–dichloroethane, decalin, ethanol, and ethanol:water (1:1). The solvent variation aims to determine the effect of the solvent on the running of the classes' rearrangement reaction.

The results showed that the Claisen rearrangement reaction and cyclization of the allyl 1–naphthyl ether compound proceeded well using 1,2–dichloroethane solvent at 80°C for 20 minutes with the help of microwave radiation (single mode). The yield resulting from the synthesis of Allyl 1–naphthyl ether is relatively high at 75.2% with a purity level of 97.3%. Purification of the Claisen rearrangement reaction was carried out by extraction using 10% NaOH, then neutralized with HCl. Furthermore, the product was extracted 3 times with chloroform. Allyl 1–naphthyl ether compounds were characterized using GC-MS to produce 2–allyl–1–naphthol as a Claisen rearrangement product, 2–methyl–2,3–dihydronaphthofuran as a cyclization product, and 1–naphthol which is the reverse product. The following

Table 1. Organic Compounds Synthesis Table Using Claisen Rearrangement

Compound Name	Methods	Temperature (°C)	Time	*Yield%*	Reference
Allyl 1-naphthyl ether	MAOS	80	20 Minutes	75.2	[16]
Prop-2'-enyloxyanthraquinones	*Reductive*	110	8 Minutes	98	[17]
Benzyl ketene acetal	*Reflux*	155	15 Hours	44	[18]
Bis-naphthopyran	*Rapid one-step*	25	24 Hours	99-100	[19]
Treprostinil	*Continuous Flow*	170	31 Hours	44	[20]

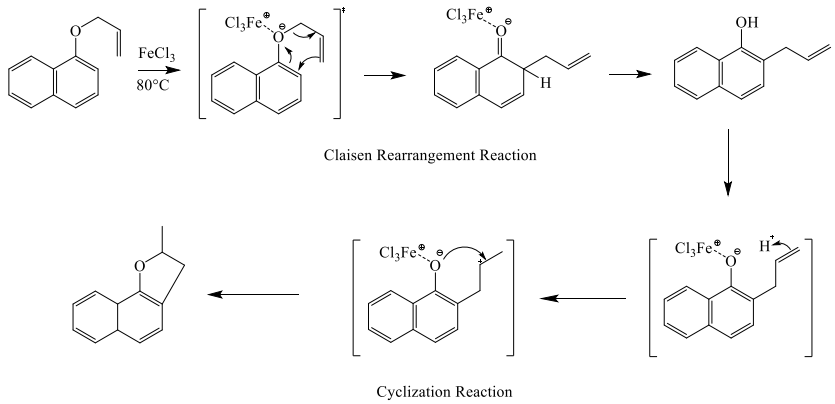

Figure 1. Claisen Rearrangement Reaction *Claisen Allyl 1-naphthyl ether*.

Claisen Rearrangement Reaction of Prop-2'-enyloxyanthraquinones

In the research conducted by Nadali et al. showed that prop–2'– enyloxyanthraquinones and 2'–chloroprop–2'–enyloxyanthraquinones can be easily rearranged to 1–hydroxy–2–(prop-2'–enyl) anthraquinones and anthrafurandiones respectively by reductive Claisen rearrangement method using iron powder[17]. The rearrangement was carried out in two ionic mixtures of [Hmim]BF4 and [Bzmim]Cl in moderate to excellent yields with short reaction times. It was also found that the prop–2'–enyloxy group was more active than 2'–chloroprop– 2'–enyloxy in this rearrangement. At 110°C, the Claisen rearrangement of 1– (prop–2'–enyloxyl) anthraquinone to 1–hydroxyl–2–(prop–2'–enyl) anthraquinone was produced in 98% yield after 8 min. However, this reaction was not successful in the absence of iron, [Hmim]BF4, or [Bzmim]Cl at the same temperature treatment giving a rearrangement product with less than 10% yield after 70 min. Moreover, the yield of this reaction decreased to 50% at 90°C, and when potassium chloride (Cl) was used instead of [Bzmim]Cl the desired product was only formed with a yield of 25% after 9 minutes.

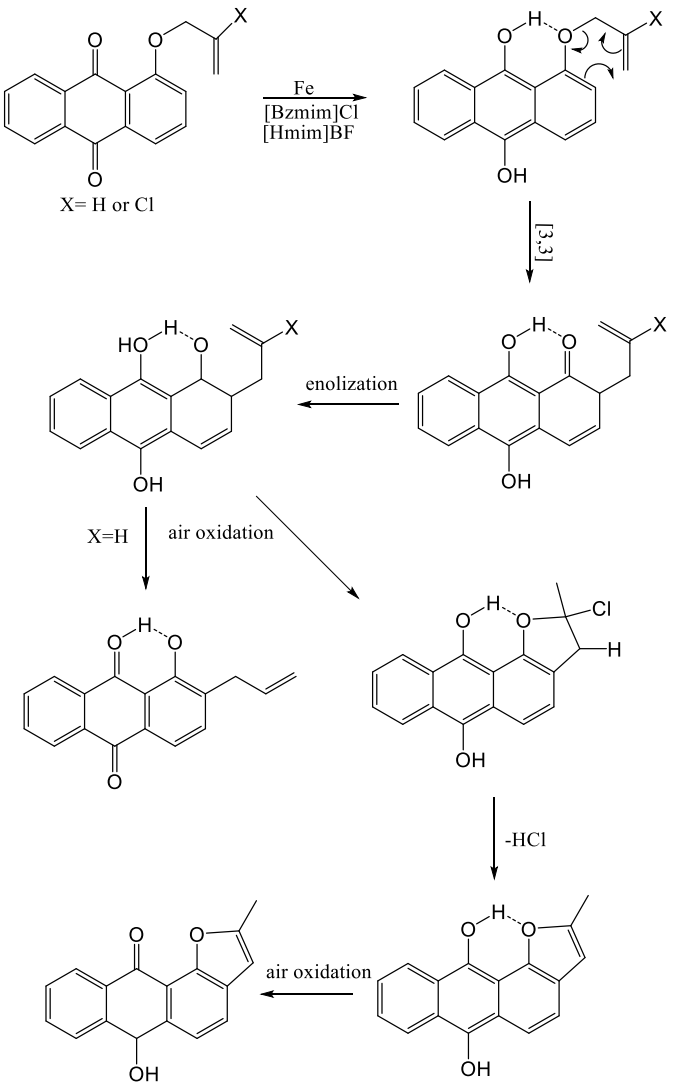

Figure 2. Mechanism of *Reductive Claisen Rearrangement of prop-2'-enyloxyanthraquinones* and *2'-chloroprop-2'-enyloxyanthraquinones* Using Fe/[Hmim]BF4/[Bzmim]Cl [17].

Claisen Rearrangement Reaction of Benzyl Ketene Acetal

Rearrangement of benzyl ketene acetal was performed by Burns et al. in 2016 using the reflux method with DMF at a temperature of 155℃ for 15 hours [18]. Rearrangement of meta-substituted benzyl ketene acetals was found to be quite regioselective, on meta-methoxy and meta-bromo substituted ketene acetals. TS14-ortho and TS14-para, yielding 15/16- para and 15/16-ortho, of which 15/16-ortho was more favorable. The class rearrangement reaction yielded 44% for 15l with ortho:para 3:2 selectivity and 24% for 16 m with ortho:para 4:1 selectivity.

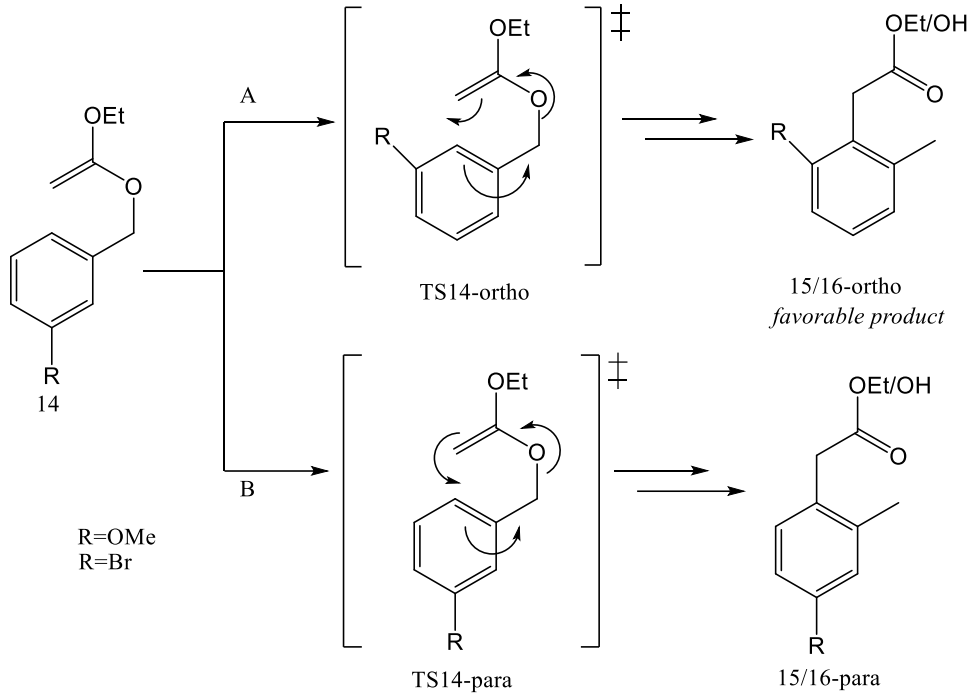

Figure 3. Mechanism of Claisen rearrangement of benzyl ketene acetal [18].

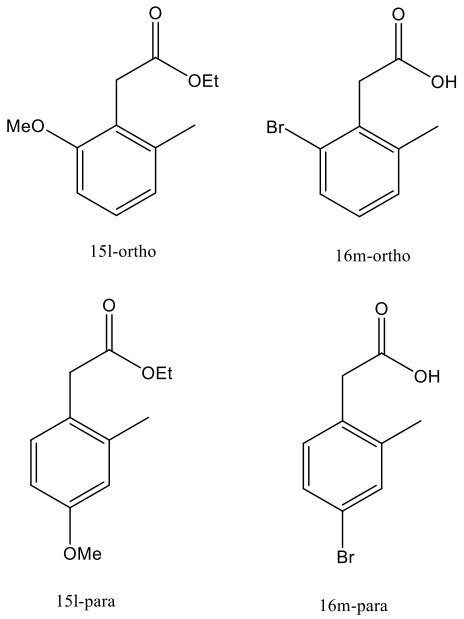

Figure 4. Product Rearrangement Claisen benzyl ketene acetate [18].

Rearrangement Reactions of bis-naphthopyran

In the research of Khder et al. a facile and efficient one-step method for the synthesis of highly active mesoporous zirconium and tin(IV)phosphate exhibiting superior catalytic activity for the synthesis of photochromic bis-naphthopyran via Claisen rearrangement was established [19]. The synthesized catalysts were characterized by different texturing and spectroscopic techniques such as XRD, FTIR spectra, SEM, TEM, and adsorption- desorption of N2 at -196°C. The results show that the zirconium phosphate sample has higher surface acidity than the tin phosphate sample, and the samples with a Zr:P ratio of 1:3 and Sn:P ratio of 1:2 show the highest surface and Brønsted acidity. The prepared catalysts exhibit excellent catalytic activity for the synthesis of bis- naphthopyran photochromes via Claisen rearrangement. A high yield (*99%) with 100% selectivity of photochromic bis-naphthopyran was obtained in a short reaction time at room temperature.

Treprostinil Rearrangement Reaction

Based on the results of research by Garcia-Lacuna et al. the synthesis of Treprostinil is carried out using the continuous flow method with two key steps namely Claisen rearrangement and Pauson-Khand reaction [20]. The Claisen rearrangement was described in scaled flow in multigram quantities while the Pauson-Khand reaction in flow was described under catalytic conditions with 5% mole cobalt and only 3 equivalents of CO. The synthesis was completed in only three steps after PKR. The synthesis was carried out at 170°C. The overall yields obtained were: 57% for aldehyde, 56% for side chain, 13.57% for fragment incorporation, and PK in the process. Then the PK reaction and the final stage gave a yield of 44%. The overall yield of Treprostinil was 14% from (S)-epichlorohydrin in 12 linear steps. A new synthesis of Treprostinil using the continuous flow method with two key steps of Claisen rearrangement and Pauson-Khand reaction showed an increase in yield in the protecting group.

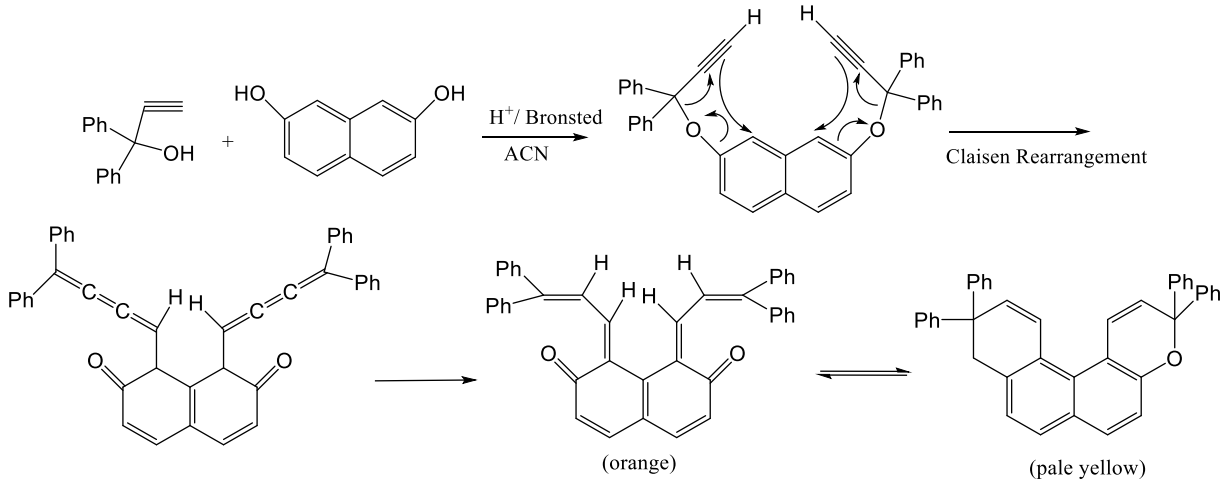

Figure 5. Claisen bis-naphthopyran rearrangement [19].

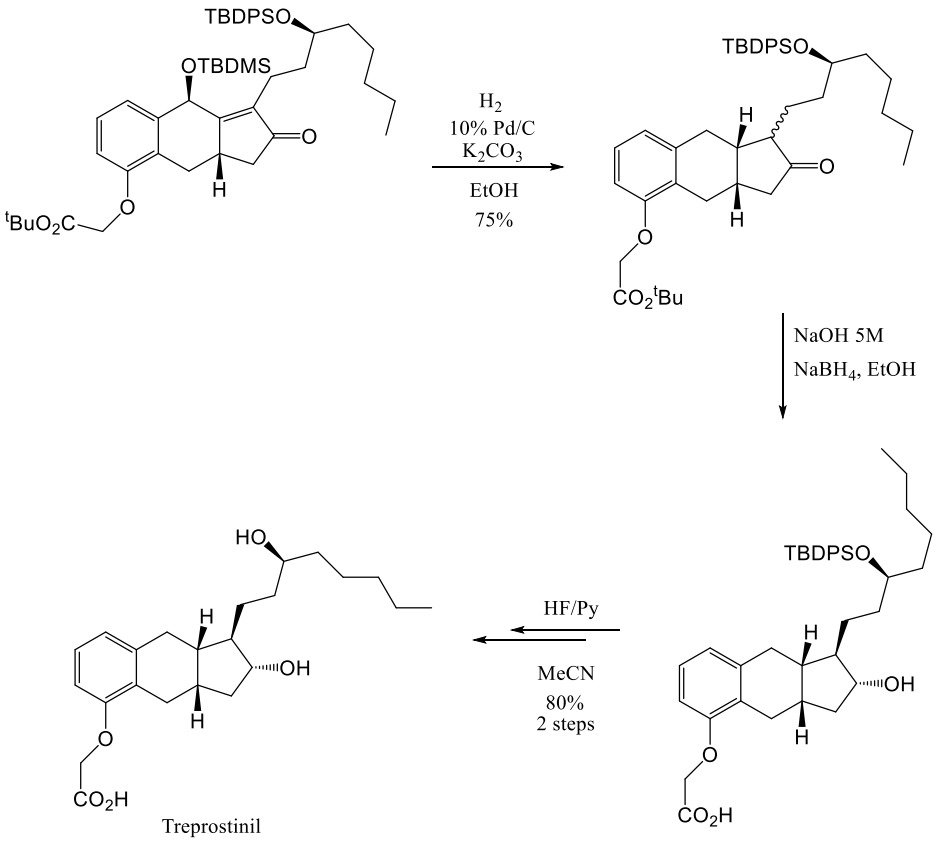

Figure 6. Completion of Treprostinil Synthesis [20].

Conclusions

The Claisen rearrangement mechanism is a synthetic method that is widely applied to organic synthesis. Several studies using the Claisen rearrangement mechanism resulted in competent organic synthesis. This can be seen through several factors such as method, temperature, time, and yield. The Claisen rearrangement mechanism still gives good results on these factors even though there are variations in the compounds used and variations in the methods combined. In theory, Claisen rearrangement is carried out at temperatures ranging from 200℃ to room temperature. This is evident from the temperatures used in several studies, where the lowest temperature is 25℃ and the highest temperature is 170℃. Then, the highest yields were 100% and the lowest yields were 44%. Organic synthesis using Claisen rearrangement produces superior-quality synthetic results.

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