Research Progress in the Synthesis of Esters

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Abstract. Ester compounds are widely found in nature and play an important role in organic synthesis. There are various methods for the synthesis of esters. This paper focuses on the simple carboxylic acid, carboxylic acid derivative and alcohol react to form ester; the reaction of alcohols and alcohols to form esters, aldehydes and alcohols to form esters, and the synthesis of esters for new catalysts and catalytic systems. The gradual realization of industrialized production has been prospected. I hope to provide more reference and inspiration to researchers.

1. Introduction
Ester compounds are widely found in nature, and many important natural products contain ester groups, such as the antitumor drug quiderone [1], a compound such as taxol [2] for the treatment of breast cancer and ovarian cancer. Therefore, the method of exploring synthetic esters has important practical significance.

With the development of society, the search for efficient and green synthetic methods has become the goal of contemporary chemists. The development of ester compound synthesis has also followed this trend. From traditional carboxylic acids, carboxylic acid derivatives and alcohols to esters, to new aldehydes and alcohols, alcohols and alcohols directly form esters, the reaction is more and more convenient. And the transition metal catalyzed aldehydes and alcohols, alcohols and alcohols directly form esters are more green and efficient.

2. Several methods for the synthesis of esters

2.1. Carboxylic acid derivatives and alcohol-forming esters
Carboxylic acids, carboxylic acid derivatives and alcohol-forming esters are conventional methods of synthesizing esters. [3] Commonly used Brnsted acid promotes the reaction, such as HCl, H2SO4, NaHSO4, H3PO4, HBF4, AcOH, camphorsulfonic acid, etc. can catalyze the reaction, the reaction formula is shown in Figure 1.
Figure 1. Reaction formula of synthetic esters

In 1971, the W. W. Jr. Lawrence group reported the relatively difficult to achieve esterification of phenols and carboxylic acids. The interaction of \( \text{H}_3\text{BO}_3 \) and \( \text{H}_2\text{SO}_4 \) can make the reaction happen smoothly [4] (Figure 2).

Figure 2. Esterification of phenols and carboxylic acids

The reaction of acid chlorides and alcohols to form esters is also widely reported. In 1990, K. Nagasawa reported the reaction of acid chloride to tert-butanol to form an ester at room temperature catalyzed by aluminum oxide [5] (Figure 3).

Figure 3. Acyl chloride reacts with tert-butanol to form an ester

2.2. Alcohols react with alcohols to form esters

The reaction of an alcohol with an alcohol to form an ester is simpler than conventional methods. The methods for producing esters of alcohols and alcohols are mainly classified into the following categories: stoichiometric oxidizing agents oxidizing alcohols and alcohol-forming esters, oxidizing agent transition metals catalyzing the formation of esters of alcohols and alcohols, and transitioning metals without oxidizing agents catalyzing the formation of esters of alcohols and alcohols. The following are introduced separately.

In 2003, the S. Bhar team discovered a solvent-free oxidation system of pyridinium chlorochromate-trialumina (PCC-Al\(_2\)O\(_3\)), which can oxidize primary alcohols to form esters [6]. Among them, PCC-Al\(_2\)O\(_3\) was prepared by adding Al\(_2\)O\(_3\) to anhydrous acetone in which PCC was dissolved and evaporating the solvent. The reaction was first carried out by dropwise adding alcohol to PCC-Al\(_2\)O\(_3\) while stirring in an ice water bath (0-5 °C), and then detecting through a spot plate at room temperature until the reaction was completed. The reaction system can form an aliphatic primary alcohol to form an ester, while the aromatic and allyl primary alcohols form an aldehyde, and the aliphatic and aromatic secondary alcohols form a ketone and the double bonds are notomerized and polymerized. The method has the advantages of simple operation, no toxic solvent, high reaction yield (68-89%), mild conditions, and suitable for substrates with various functional groups (Figure 4).

Figure 4. Primary alcohol is oxidized to PCC-Al\(_2\)O\(_3\) to form an ester
In 2014, the P. Phukan group discovered a metal-free N, N-dibromo-p-toluenesulfonamide (TsNBr₂) catalyzed aldehyde or alcohol oxidation methyl esterification reaction [7]. The reverse method is a simple and efficient reaction system carried out at room temperature, and is suitable for simple alcohols such as ethanol, n-propanol and the like (Figure 5).

$$\text{R-OH} \xrightarrow{\text{TsNBr}_2, \text{K}_2\text{CO}_3, \text{rt}} \text{O} \xrightarrow{\text{MeOH, rt}} \text{R-H}$$

Figure 5. TsNBr₂ catalyzed aldehyde or alcohol oxidation methyl esterification reaction

In 2013, Y. Y. Wei Group studied the solvent-controlled copper-catalyzed oxidation of benzyl alcohol to ester [8]. CuI is a catalyst, and tert-butyl hydroperoxide (DTBP) is an oxidizing agent, and an ester can be formed without a solvent (Figure 6).

$$\text{R-OH} + \text{R′OH} \xrightarrow{\text{CuI (10 mol%), L (10 mol%), DTBP (4 mol), rt}} \text{R′O}$$

Figure 6. Solvent-controlled copper-catalyzed oxidation of benzyl alcohol to ester

In 2007, the T. Ikariya group studied the reaction of 1, 4-diol oxidation to lactone catalyzed by Cp*Ru(PN) complex [9]. The reaction Cp*Ru (PN) was used as a catalyst, acetone was used as a hydrogen acceptor, and t-BuOK was used as a base to carry out a reaction at 30 °C to obtain γ-butyrolactone (Figure 7).

$$\text{Rn-OH} \xrightarrow{\text{Cp*Ru(RN) cat. acetone >1,000 TOF/h (30 °C)}} \text{Rn}$$

Figure 7. Oxidation of 1, 4-diol to lactone catalyzed by Cp*Ru (PN) complex

The transition-metal-catalyzed reaction of the oxidant-free alcohol and the alcohol to ester does not require the addition of an oxidizing agent as a hydrogen acceptor, but the reaction is achieved by releasing hydrogen. In 1981, the T. Naota group reported that the hydrogen-free acceptor Ru catalyzes the reaction of alcohols with alcohol to form esters [10]. RuH₂(PPh₃)₄ was used as a catalyst, and toluene was used as a solvent. Under reflux of argon at 180 °C for 24 h, a good yield was obtained. Both aliphatic and aromatic alcohols can be reacted, and the substrate of the reaction is widely applicable. By adding acetone as a hydrogen acceptor in this reaction, the reaction yield can be improved (Figure 8).

$$\text{Rn-OH} \xrightarrow{\text{RuH}_2\text{(PPh}_3\text{)}_4 \text{ (2 mol%), PHMe, 180 °C, 24 h}}} \text{Rn}$$

Figure 8. Reaction of the oxidant-free alcohol and the alcohol to ester

2.3. Aldehyde and alcohol react to form ester
A method for the oxidation of an aldehyde and an alcohol to form an ester by a stoichiometric oxidant is widely reported. In 1968, A. Nishihara and I. Kubota discovered a hydrogen peroxide-sulfuric acid catalytic oxidation system [11]. The system actually uses persulfate (H₂SO₅) to convert benzaldehyde
to methyl benzoate. Among them, persulfuric acid, also known as caroic acid, is obtained by adding hydrogen peroxide at 15 °C to concentrated sulfuric acid. The reaction mechanism proposed by him is: aldehyde and alcohol are converted into intermediate hemiacetal A under acidic conditions, A further produces intermediate B under the action of persulfuric acid, and B removes one molecule of sulfuric acid to obtain an ester (Figure 9).

$$\text{CHO} \quad \xrightarrow{\text{H}_2\text{SO}_5 \ (1 \text{ mol})} \quad \text{COOMe}$$

**Figure 9.** Conversion of benzaldehyde to methyl benzoate oxidized by H$_2$SO$_5$

In 2003, the H. Sharghi group proposed the Al$_2$O$_3$/MeSO$_3$H oxidation system [12]. The monoesterification of aldehydes and different diols can be achieved by stirring the system at 80 °C for 2-10h. The alcoholic hydroxyl groups of the amino alcohol and the secondary alcohol can also participate in the reaction (Figure 10).

$$\text{CHO} \quad + \quad \text{HO-\text{OH}} \quad \xrightarrow{\text{Al}_2\text{O}_3 \ (3 \text{ mol}), \text{MeSO}_3\text{H} \ (15 \text{ mol})} \quad \text{O-O-\text{OH}}$$

**Figure 10.** Monoesterification of aldehydes and different diols

In 2004, Y. X. Qi group studied the oxidative esterification of aldehydes by S·SnO$_2$/SBA-1-H$_2$O$_2$ [13]. The reaction H$_2$O$_2$ is an oxidant, and SBA-1 is a matrix of sulfurized tin dioxide (S·SnO$_2$) as a catalyst. The reaction is carried out in an alcohol solution at 50 °C for 4-18 h to obtain the corresponding ester. It has been found in the extension of the substrate that the aldehyde can react well with various alcohols, and the alcohol having a double bond and a triple bond can also be reacted, and the double bond and the triple bond are not converted (Figure 11).

$$\text{R}_1\text{H} \quad + \quad \text{R}_2\text{-OH} \quad \xrightarrow{\text{S·SnO}_2/\text{SBA}, \text{H}_2\text{O}_2, \text{HClO}_4} \quad \text{O-O-R}_1\text{O-R}_2$$

**Figure 11.** Oxidative esterification of aldehydes by S·SnO$_2$/SBA-1-H$_2$O$_2$

Transition-metal-catalyzed aldehyde-free and alcohol-forming reactions directly form esters that produce many by-products [14]. It is therefore necessary to add an oxidizing agent to increase the selectivity. In 1973, M. Hidai discovered that RuCl$_2$(C$_{12}$H$_{18}$) can directly catalyze the formation of esters of aldehydes and alcohols [46]. RuCl$_3$H$_2$O, [RhCl(C$_2$H$_4$)$_2$]$_2$, Rh(acac)(C$_2$H$_4$)$_2$, RhCl(PPh$_3$), IrCl(CO)(PPh$_3$), RuCl$_4$(C$_3$H$_10$) and other catalysts were screened and found to be catalyzed by these catalysts. The reaction, but RuCl$_2$(C$_{12}$H$_{18}$) has the best catalytic efficiency. Although RuCl$_2$(C$_{12}$H$_{18}$) has the highest catalytic efficiency, many by-products are reacted, and the yield is only 10% (Figure 12).

$$\text{H}_2\text{C}≡\text{CHCHO} \quad + \quad \text{C}_2\text{H}_5\text{OH} \quad \xrightarrow{\text{RuCl}_2(\text{C}_2\text{H}_{18})} \quad \text{H}_2\text{C}≡\text{CHCOOC}_2\text{H}_5$$

**Figure 12.** Reaction of an aldehyde-free aldehyde with an alcohol to form an ester

In 2007, the C. J. Li group discovered copper and indium bimetallic catalyzed aldehyde and alcohol esterification systems [15]. The system uses Cu(ClO$_4$)$_2$·6H$_2$O and InBr$_3$ as catalysts, tert-butyl hydroperoxide (TBHP) as oxidant, excess alcohol, and the corresponding esters can be obtained by reacting aliphatic and aromatic aldehydes at 100 °C for 16 h (Figure 13).
In 2005, the S. ichi Kiyooka group discovered the oxime-catalyzed oxidative esterification of aldehydes and enols [16]. The reaction was carried out by using K$_2$CO$_3$ as a base and [IrCl(cod)]$_2$ as a catalyst, and reacting in toluene at room temperature for 12 h to obtain an esterified product. The reaction conditions are mild and have a certain substrate suitability, but the selectivity is slightly poor (Figure 14).

In 2006, the C. Wolf group used di-tert-butylphosphoryl palladium chloride (PoPd) and siloxane to complete the oxidative esterification of aldehydes [17]. The reaction was carried out using PoPd as a catalyst, and 1.1 eq of tetramethoxysilane and 1.3 eq of tetrabutylammonium fluoride (TBAF) were added, and the corresponding methyl ester product was obtained by reacting in acetonitrile at 50°C for 24 h. The reaction conditions are mild, with higher yields for secondary alcohols than known reaction systems, and the use of transition metals and fluorosilanes is avoided (Figure 15).

In 2012, A. W. Lei Group discovered a palladium-catalyzed aldol formation system using benzyl chloride as an oxidant [18]. Among them, [PdCl$_2$(PPh$_3$)$_2$] is a catalyst, PhCl is an oxidant, and K$_2$CO$_3$ is a base in THF at 60°C for 20 h to obtain an esterified product. The reaction ratio of the reaction aldehyde and the alcohol is 1:1, the amount of the oxidizing agent is small, the selectivity is good, the yield is high, and the solvent can be efficiently carried out without a high S/C (Figure 16).

3. Conclusion
Ester compounds have become the star of anticancer drugs and have been included in the history of medicinal chemistry. Therefore, the synthesis of ester compounds has become one of the directions of medicinal chemistry research. In this paper, the synthesis methods commonly used in ester compounds in recent years are summarized as follows: (1) carboxylic acids and their derivatives and alcohol-forming esters; (2) alcohols and alcohols to form esters; (3) aldehydes and alcohols ester. The method for producing esters of alcohols and alcohols is mainly divided into: a stoichiometric oxidizing agent oxidizing an alcohol and an alcohol to form an ester, an oxidizing agent transition metal catalyzing an
alcohol and an alcohol to form an ester, and an oxidizing agent-free transition metal catalyzing an alcohol and an alcohol forming an ester; and the alcohol and the aldehyde forming an ester mainly divided into stoichiometric oxidants oxidized aldehydes and alcohol-forming esters, transition metal catalyzed by oxidant aldehydes and alcohol-forming esters. With the development of synthetic ester reactions, more and more reaction systems have been developed, which will have a major impact on organic synthesis, and the synthesis of esters using new catalysts and catalytic systems will gradually achieve industrial production. Human production and life have brought about tremendous changes.

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