

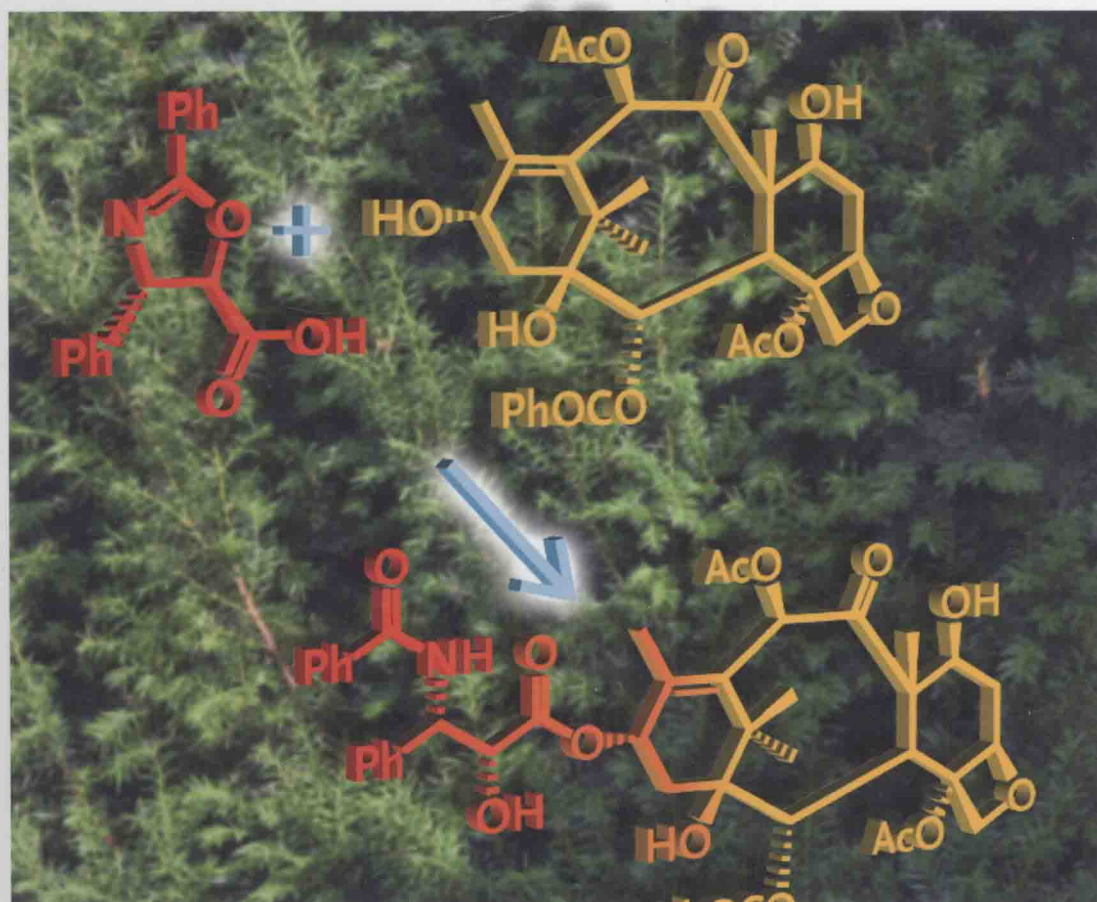
Junzo Otera and Joji Nishikido

WILEY-VCH

Esterification

Methods, Reactions, and Applications

Second, Completely Revised and Enlarged Edition



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Esterification

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Preface

Few would dispute that the synthesis of esters has played a most important role in organic synthesis from its infancy. This importance stemmed from its utility in diverse fields both in the laboratory and in industry. Ester moieties, irrespective of whether acyclic and cyclic, constitute major backbones, as well as functional groups of chemical significance, in numerous natural products and synthetic compounds. The essential feature of esterification that particularly distinguishes it from other reactions lies in its broad utilization in industry. Just a brief chronological look quickly reminds us of aspirin (acetyl salicylic acid), fatty acid esters, polyesters, macrolides, and so on. In addition to being essential molecular components in their own right, ester groups also play versatile temporary roles in organic synthesis for protection of carboxylic acids and hydroxy groups. The synthesis of natural products, especially macrolides, sugars, and peptides, depends heavily on acylation technology.

Being carboxylic acid derivatives, esters are largely produced from the reactions between the corresponding acids and alcohols. Transformation from one ester into another (transesterification) is also useful. On the other hand, since esters are also derivatives of alcohols, ester synthesis is also important from the standpoint of alcohol chemistry, such as acylation. A variety of routes to arrive at esters are therefore feasible, and numerous methods have been reported. Surprisingly, though, no book focused solely on 'esters' has been available up to now, esterification or transesterification usually being included in many books as a sub-class of functional group transformations. Obviously, this is not a fair treatment if the central position of (trans)esterification in organic synthesis is taken into account. Why did such biased circumstances arise? A number of reasons can be identified immediately, but only a few representatives among them are given here. Since (trans)esterification has such a long history and the reaction itself is simple, many people, especially in academia, take it for granted that little room is left for further scientific improvements. In industry, on the other hand, (trans)esterification still has continuing significance, and many new technologies, being classed as know-how, therefore remain undisclosed. Since the utility of (trans)esterification has spread into diverse fields, it is indeed laborious to cover the whole, as even those people who are deeply involved in the (trans)esterification fields, regardless of whether in academia or in industry, have rather limited knowledge about what is

going on outside the very narrow disciplines close to them. Despite such undesirable circumstances, (trans)esterification has in fact been, and is still undergoing, extensive innovations. It is the aim of this book to inform a broad range of chemists and technicians on the state of the art relating to both fundamental ideas and practical aspects of (trans)esterification.

The book consists of two parts. The first part thoroughly reviews the (trans)esterification reaction, from conventional approaches to the most up-to-date progress in terms of reaction patterns, catalysts, reaction media, etc., so that readers may acquire general, basic knowledge of the reaction. In addition, those wanting to survey suitable methods for a specific target will find great help from consulting this part. A number of 'Experimental Procedures' given may help readers judge which reactions are suitable for their purpose.

Synthetic applications of (trans)esterification are the subject of Part II. These reactions, many of which may have already appeared in Part I, are reorganized according to their respective synthetic purposes. Various aspects of interest to synthetic chemists are summarized, followed by an overview of industrial utilization.

Because of its long history, it has been impracticable to survey the literature of esterification completely from the beginning. A full survey from 1990 has therefore been made by use of commercial databases, while reference works appearing before 1990 have been selected arbitrarily depending on their importance. I believe that this treatment is fully acceptable, namely to cover the literature that is of basic significance and to represent recent progress to meet the requirements for 'modern esterification.' Resulting from this, we encountered more than 5000 references, but for reasons of space not all of them could be accommodated in the text of this book. Only examples selected in terms of fundamentality and generality have been taken, to provide a comprehensive view of the overall aspects as broadly as possible. All collected references have been placed in a database library, a copy of which is provided on disc at the back of this book. Those who wish to obtain more detailed information will be able to consult this library through keyword access.

Last, but not least, I would like to express my sincere appreciation to Miss Masayo Kajitani, who contributed greatly to the literature survey and the illustrations. Without her collaboration and patience, this book might have not been completed.

Okayama, November 2002

Junzo Otera

Preface to the Second Edition

More than five years have passed since the first edition was published. Esterification has continued to advance in the meantime, proving its continuing importance in organic synthesis and chemical industry. A literature survey covering the period 2002–2007 performed with the aid of SciFinder revealed about 5300 relevant references, simple enumeration of which is not the purpose of the second edition, of course. Only about 500 of these references, which have particular scientific or practical merits, have been newly included in this volume, which follows the original format of the first edition. It is of interest to note that nearly half of them are associated with green chemistry, reflecting rapidly growing environmental concerns. This trend is clearly seen in the accelerated development of solid acid catalysts and enzymes. Replacement of conventional organic solvents by new reaction media such as water, fluorous solvents, ionic liquids, and supercritical solvents has also become very popular for the same reason. Esterification has acquired further innovation from the engineering side. As a consequence of its remarkable progress, Section 7.4, 'New Technologies,' now appears in this edition.

Chapter 8, 'Industrial Uses,' has also been expanded. First, ethyl acetate and acrylic esters as fundamental raw materials are briefly surveyed (Sections 8.1 and 8.2, respectively). As biodiesel fuel has recently undergone dramatic industrial development, an overview of this topic is presented in Section 8.5. Industrial aspects of macrolide synthesis are also newly covered in a separate section (Section 8.7). Furthermore, a number of additions have been made to other sections in this chapter.

For this new edition, a thorough literature survey and many new illustrations were required. These painstaking tasks were carried out to perfection by Ms Satoko Kira and Ms Hisaji Dozen, to whom the authors would like to express their sincere appreciation.

Okayama, November 2009

On behalf of the authors,
Junzo Otera

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Introduction

The biggest problem frequently encountered in (trans)esterification technology arises from the fact that in the majority of cases a reversible reaction is involved. To bias the equilibrium to the product side, one of the reactants must be used in excess and/or one of the products must be removed constantly during the reaction. Use of a nonequilibrium reaction approach, with the aid of activated reactants such as acid anhydrides and halides or alkoxides, can be effective to circumvent the problem on some occasions, but is not always general. Ester synthesis reactions are usually conducted with the aid of acid or base catalysts, and so the employment of catalysts or promoters that are suitably active but also compatible with other functional groups is of great importance. Progress has been made to overcome these problems in (trans)esterification reactions.

Esterification can be regarded as the transformation of carboxylic acids or their derivatives into esters, a procedure which is carried out in many natural products syntheses, in the protection or kinetic resolution of carboxylic acids, and in the fatty acids industry. However, the converse reaction – transformation of alcohols into esters, as in protective acylation of hydroxy groups, kinetic resolution of alcohols, and so on – is equally important. The normal substrate/reagent relationship cannot therefore be straightforwardly applied to esterification. Moreover, in intramolecular cases (lactonization) and polycondensation, both function as equal partners. In Chapter 1 the alcohol component is regarded as the substrate, because modifications of carboxylic acids are available in greater variety. Of course, such classification is not strict: the carboxylic acid component might as well be taken as a substrate in, for instance, the direct reaction between neat alcohol and carboxylic acid. In any event, the chapter is subdivided into sections according to the means by which the carboxylic acid is modified. Each section is then further sub-classified according to the activation modes.

Tin alkoxides, together with some other metal alkoxides, are useful for selective acylation of polyols and, in particular, play an important role in sugar chemistry. This subject is grouped separately in Chapter 2.

In Chapter 3, the carboxylic acid component is treated as the substrate, reacting with various reagents other than alcohols. Chapter 4 deals with interconversion between different esters.

The first two chapters in Part II, Chapters 5 and 6, are both associated with chirality. In response to the increasing need for optically active compounds in modern synthetic chemistry, great progress has been achieved in ester technology, serving for the production of enantiomerically enriched or enantiomerically pure alcohols and carboxylic acids through kinetic resolution and desymmetrization.

Chapter 7 covers miscellaneous topics of great significance in terms of synthetic utility and various selectivities. Natural product syntheses in which esterification has played a crucial role are also described.

Finally, in Chapter 8, industrial uses of esterification technology are examined. Since many currently operational (especially state-of-the-art) processes are 'know-how,' which means that they are effectively veiled in darkness, it is not an easy task to give any kind of detailed account of them here. At best, we can outline salient points that are either common knowledge or available from the literature. Despite such limitations, the reader should be able to form an idea of how and where esterification is utilized in practice.

Part One Methodology

1

Reaction of Alcohols with Carboxylic Acids and their Derivatives

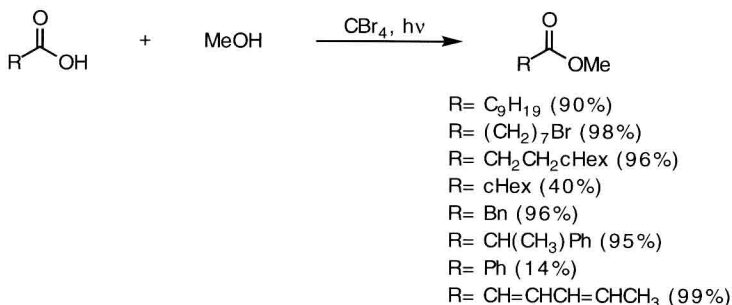
1.1

Reaction with Carboxylic Acids

1.1.1

Without Activator

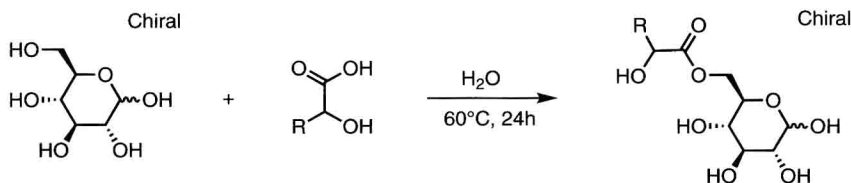
Although the direct reaction between alcohol and carboxylic acid is conventionally conducted under acid or base catalysis conditions, the catalyst-free reaction is more desirable. This requirement is satisfied when the reaction is carried out at high temperatures. For example, propanol or hexanol can be treated with various aliphatic carboxylic acids (1.35 equiv.) in an autoclave at 150 °C to furnish esters in poor to excellent yields (Scheme 1.1) [1]. The reaction is strongly influenced by the reaction temperature; the yield of propyl acetate is only 18% at 85 °C.



Scheme 1.1

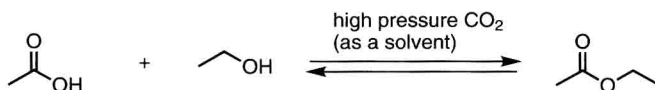
Interestingly, condensation between sugars and α -hydroxycarboxylic acids can be performed in water (Scheme 1.2) [2]. The reaction takes place at 60 °C, regioselectively on the primary hydroxy groups of mannose, galactose and glucose. The avoidance of any catalysts or additives allows the instant application of the products in food technology and cosmetic formulation.

Experimental Procedure Scheme 1.2 [2] General procedure: A mixture of hydroxycarboxylic acid, carbohydrate, and water is heated to 60 °C in air for 24 h. To isolate the product as a pure compound for characterization, the reaction mixture is extracted twice with diisopropyl ether, the solvent is removed *in vacuo*, and the residue is chromatographed on silica gel (CH₂Cl₂/MeOH; 85 : 15).



Scheme 1.2

The equilibrium in the reaction between ethanol and acetic acid can be shifted in favor of the ester by application of CO₂ pressure (Scheme 1.3) [3]. The ester yield is increased from 63% in neat solution to 72% in CO₂ at 333 K/58.6 bar. This outcome is far from satisfactory, though the possibility does suggest itself that the equilibrium may be improved by changing the reaction conditions.



Scheme 1.3

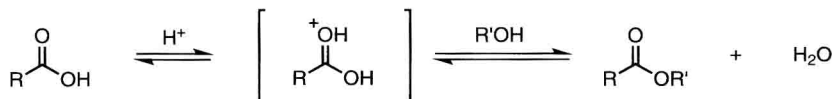
On the whole, the catalyst-free reaction is ideal but difficult to achieve. Some special conditions are necessary, and employable reactants are rather limited. Nonetheless, it is obvious that this line of technology should be advanced more extensively in the context of green chemistry.

1.1.2

Acid Catalysts

1.1.2.1 Brønsted Acids

Since acid catalysis is one of the most popular methods for esterification, numerous papers are available. When the substrates are acid-resistant, the reaction is usually carried out in the presence of a Brønsted acid such as HCl, HBr, H₂SO₄, NaHSO₄, ClSO₃H, NH₂SO₃H, H₃PO₄, HBF₄, AcOH, camphorsulfonic acid, etc. (Scheme 1.4).



Scheme 1.4

In cases in which the acidity is not high enough to trigger the desired reaction, the acid is combined with an activator. For example, the lactonization shown in Scheme 1.5 proceeds sluggishly with HCl only, but the reaction is effected smoothly in the