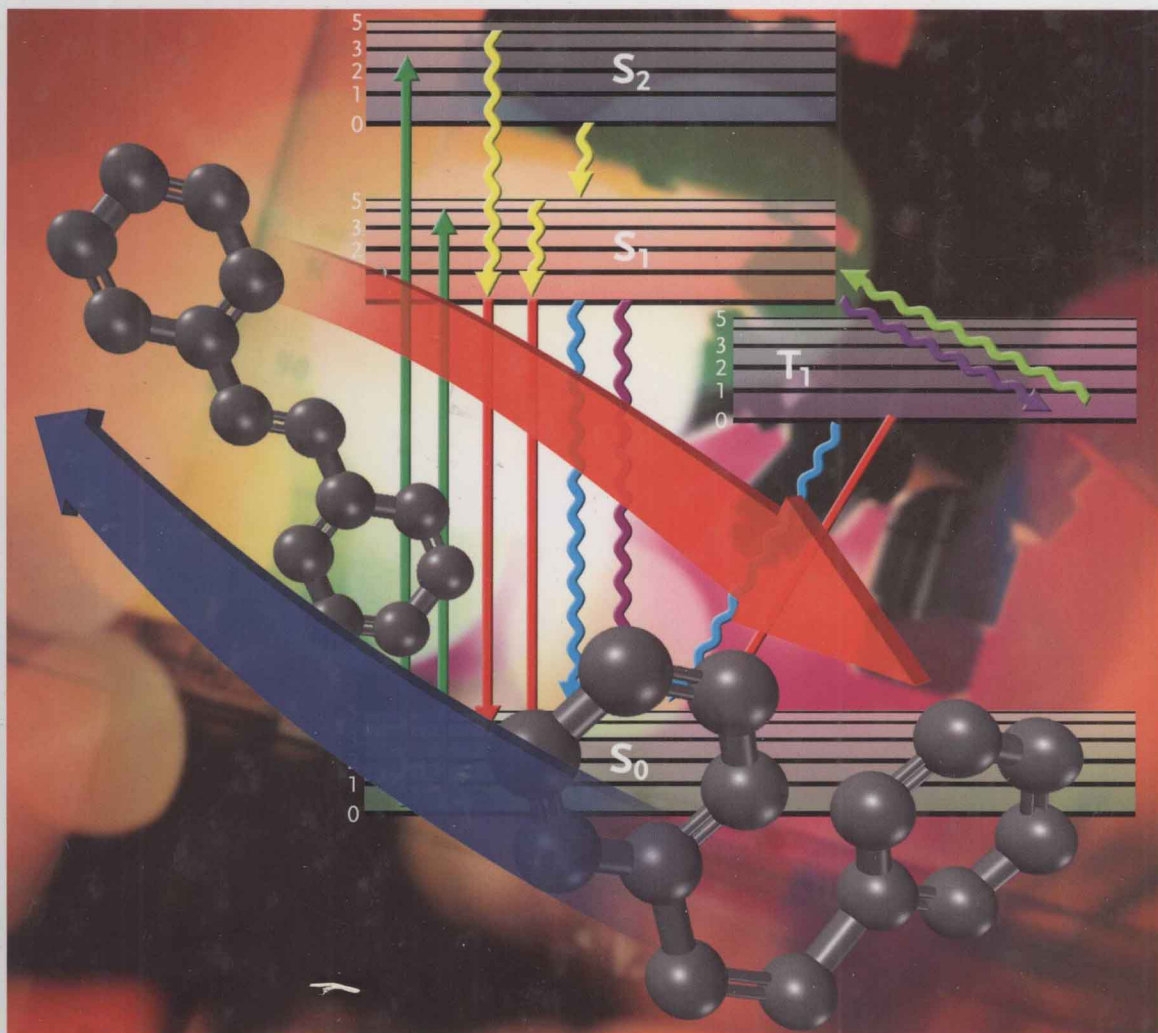


Gertz Likhtenshtein

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Stilbenes

Applications in Chemistry, Life Sciences
and Materials Science



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and Materials Science



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Preface

Stilbenes and their derivatives, stilbenoids, form a multidisciplinary field that combines many important branches of chemistry, biology, and physics. This field is under active investigation now. The number of publications on stilbenes available on Internet has reached about 32 000. Classical and modern synthetic organic chemistry (more than 6300 articles), providing a whole arsenal of stilbenes of different structures, is paving the way for numerous fundamental research and practical applications. Unique features of this class of compounds, including a combination of fluorescence, phosphorescence, photochrome, photochemical, and photophysical properties, have long been a matter of great interest to researchers. Specifically, recent years have seen the accumulation of new facts and ideas in the following areas: (i) stilbenes have proved to be convenient models ("proving ground") for experimental and theoretical investigations of detailed mechanisms of photochemical and photophysical processes including photochromism and multiphonon phenomena; (ii) stilbenoids are naturally present in plants (e.g., resveratrol and pterostilbene) and make an important contribution to biochemical and physiological processes in plants and have been used as drugs and antitumor agents; (iii) stilbene derivatives have been used as molecular probes and labels for investigation of dynamic properties of proteins and biomembranes; (iv) stilbenes are used as dyes, brighteners, whiteners of paper and textile, and photobleachers; (v) stilbene and its combination with polymers and inorganic materials have been made a basis for numerous optical and measuring instruments, devices, and apparatuses for dye lasers, organic solid lasers, and scintillators, phosphorus, neutron, and radiation detectors, electrophotographic photoconductor and image-forming apparatus, and photochromic, light-transmitting, dichroic, electroluminescent nonlinear optic, and organic-inorganic hybrid multichromophoric optical limiting materials.

This book will concisely cover practically all aspects of stilbenes: the chemical synthesis, the modern methods of investigations, their chemical, photochemical, and photophysical properties, their biological role, their use as therapeutic agents, and the instrumentation and materials.

This book is not intended to provide an exhaustive survey of each topic but rather discusses their theoretical and experimental backgrounds, and recent developments.

The literature on stilbenes is so vast, and many scientists have made important contribution in the area, that it is impossible to give a representative set of references in the space allowed for this book. The author apologizes to those he has not been able to include. More than 1100 references are given that should provide a key to essential relevant literature.

Fundamentals, classical and new methods of preparation, and basic chemical properties of stilbenes form the main topics of Chapters 1 and 2. In Chapters 3 to 5, the general theoretical and experimental backgrounds and recent results are explained for photophysical and photochemical properties of stilbenes stressing a detailed mechanism of photoisomerization. Advances in traditional and new areas of construction and investigation of photophysical and photochemical materials on the basis of stilbenes form the subject of Chapter 6. Chapters 7 to 9 consider biochemical, biomedical, therapeutic, and clinical applications of stilbenes, that is, in areas that appear to be of great importance for human well-being. Chapter 10 discusses fundamentals and recent results of using stilbenes as probes for investigating molecular structure, dynamics, and functional activity of proteins, enzymes, and biomembranes and real-time analysis of biologically active compounds. Chapter 11 describes the recent advances in modern absorption, fluorescence, and vibration techniques and related areas that to a considerable extent were stimulated by the growing requirements of stilbene applications.

This monograph is intended for scientists working on chemistry, physics, and biology of stilbenes and related areas such as optical materials and devices production, molecular biophysics, plant biochemistry, biomedicine, and pharmacology. The book can also be used as a subsidiary manual for instructors and graduate and undergraduate students of university physics, biochemistry, and chemistry departments.

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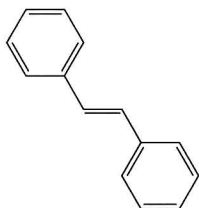
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Stilbenes Preparation and Analysis

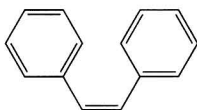
1.1

General

The name for stilbene (1,2-diphenylethylene) was derived from the Greek word *stilbos*, which means shining. There are two isomeric forms of 1,2-diphenylethylene: (*E*)-stilbene (*trans*-stilbene), which is not sterically hindered, and (*Z*)-stilbene (*cis*-stilbene), which is sterically hindered and therefore less stable.



trans-stilbene



cis-stilbene

(*E*)-Stilbene has a melting point of about 125 °C, while the melting point of (*Z*)-stilbene is 6 °C. Stilbene is a relatively unreactive colorless compound practically insoluble in water [1]. *trans*-Stilbene isomerizes to *cis*-stilbene under the influence of light. The reverse path can be induced by heat or light. The stilbene feature is associated with intense absorption and fluorescence properties, which correspond to the excitation of π -electrons of the conjugated ethenediyl group into π^* orbitals, as well as some other dynamic processes. The excited singlet state behavior of *trans*-stilbene is governed by fluorescence from the S_1 state that effectively competes with isomerization. This phenomenon of photochromism, namely, *trans*–*cis* photoisomerization of stilbene derivatives, can be readily monitored by a single steady-state fluorescence technique. A necessary stage in the olefinic photoisomerization process, in the singlet or triplet excited state, involves twisting (about the former double bond) of stilbene fragments relative to one another. The chemistry and photochemistry of stilbenes have been extensively investigated for decades and have been reviewed [2–25].

Stilbene derivatives are synthesized relatively easily, are usually thermally and chemically stable, and possess absorption and fluorescence properties that are

convenient for monitoring by relevant optical techniques. Stilbenes are widely used in the manufacture of industrial dyes, dye lasers, optical brighteners, phosphor, scintillator, and other materials. They are playing an increasingly prominent role in the area of photophysical, photochemical, biophysical, and biomedical investigations.

Hydroxylated derivatives of stilbene (stilbenoids) are secondary products of heartwood formation in trees that can act as phytoalexins (antibiotics produced by plants).

Because of the chemical stability of phenyl moiety of 1,2-diphenylethylene, stilbene is not a suitable starting compound for synthesis of stilbene derivatives. In order to form more complex molecules, it is necessary to introduce more reactive functional groups.

1.2

Classical Methods and Their Development

Many synthetic routes to stilbene derivatives have been reported, and only most important methods, which were used in the total synthesis, will be considered in this section. Figure 1.1 summarizes the five most important methods for forming the C=C bond of the 1,2-ethenediyl unit in stilbenes.

The following classical methods will be described in this section:

1. Aldol-type condensation
2. Siegrist method
3. Wittig–Horner reaction
4. Heck reaction
5. Negishi–Stille reactions
6. Barton–Kellogg–Staudinger reaction
7. McMurry reaction
8. Perkin reaction

1.2.1

Aldol-Type Condensation

Aldol-type condensation of an aromatic aldehyde with activated methylarene or phenylacetic acid is a useful reaction for preparing stilbene derivatives. Starting from *para*-substituted toluenes or *para*-substituted aromatic aldehydes, one can obtain 4,4'-disubstituted stilbenes. This reaction is relatively simple but has low yield. As an example, condensation of 2,4-dinitrotoluene and 4-nitrophenylacetic acid with aromatic aldehyde was studied [26]. The reaction involves carbanion addition to the carbonyl group. The carbanion is formed by the extraction of proton from the active methylene group of 2,4-dinitrotoluene by the base (usually, piperidine). The carbanion then adds to carbon atoms of the carbonyl group of the aldehyde. The reaction will therefore be facilitated by the ease of both the formation of the

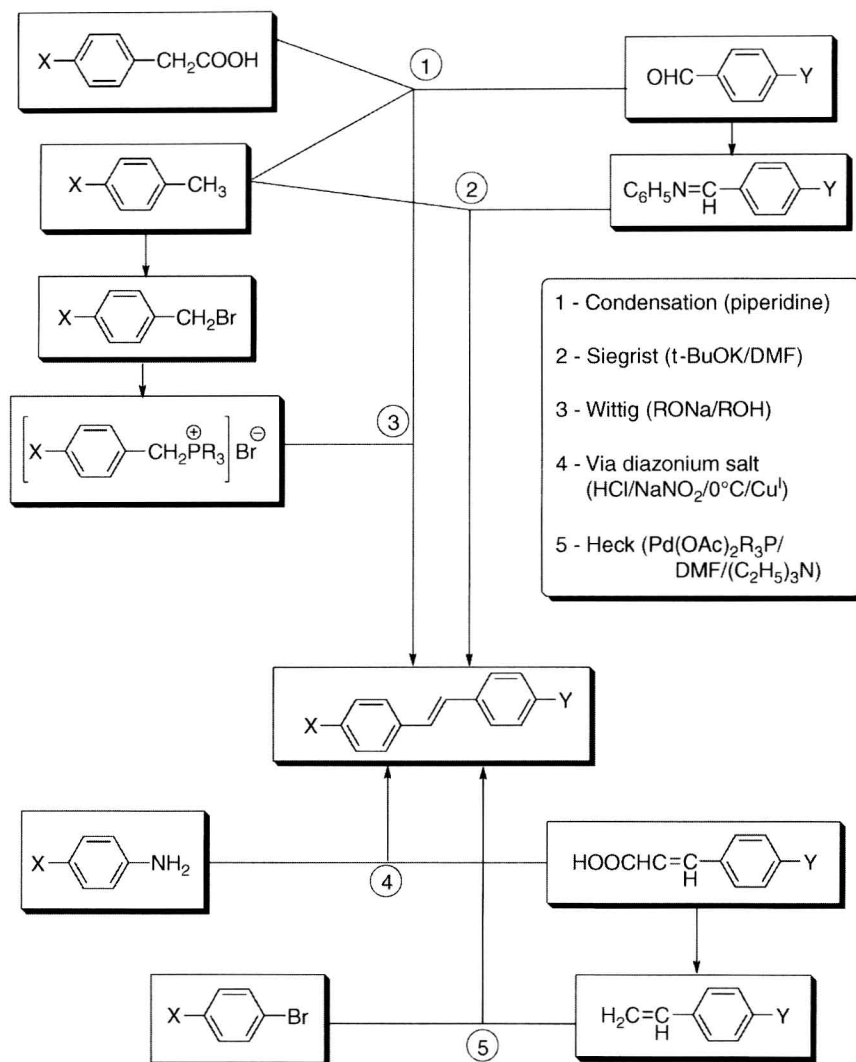


Figure 1.1 The most important synthetic routes to stilbene compounds. (Reproduced with permission from Ref. [24].)

relatively stable carbanion and the formation of the carbonium ion, which is obtained by the migration of p-electrons from carbonyl to the oxygen atom.

1.2.2

Siegrist Method

The total yield of the Siegrist method (Figure 1.1) [27] is often inferior to those of the other four methods – its main advantage is its remarkably high selectivity.

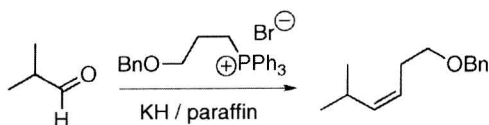


Figure 1.2 Wittig reaction using potassium hydride in paraffin. (Reproduced with permission from Ref. [30].)

For example, the synthesis of 4-methoxy-4-methyl stilbene showed that the selectivity of *cis*-configuration is 100 times more [28]. The decisive factor here in this reaction is the anti-elimination (E2) from the least energetic conformation.

1.2.3

Wittig Reaction

The Wittig reaction is the reaction of an aldehyde or ketone with a triphenyl phosphonium ylide to give an alkene and triphenylphosphine oxide. The Wittig reaction was discovered in 1954 by Georg Wittig and described in his pioneering publication titled “Über Triphenyl-phosphin-methylene als olefinbildende Reagenzien I” [29]. A recent example of the Wittig reaction is shown in Figure 1.2.

The Wittig reaction has proved to be quite versatile in the preparation of different substituted stilbenes [31–36]. This reaction is not sensitive to atmospheric oxygen, thus allowing simpler experimental procedures. It furnishes the *trans*-isomer in the stereospecific reaction. Moreover, the *trans*-isomer can be separated from the *cis*-isomer in the course of reaction because it is less soluble in the reaction solvent (usually, methanol, if sodium/lithium methoxide is used as a base) and precipitates on standing.

The Horner–Wadsworth–Emmons reaction (or HWE reaction) is the reaction of stabilized phosphonate carbanions with aldehydes (or ketones) to produce predominantly *E*-alkenes. In 1958, Horner published a modified Wittig reaction using phosphonate-stabilized carbanions [32]. Wadsworth and Emmons further defined the reaction [33]. Compared to phosphonium ylides used in the Wittig reaction, phosphonate-stabilized carbanions are more nucleophilic and more basic. Likewise, phosphonate-stabilized carbanions can be alkylated, unlike phosphonium ylides. The dialkylphosphate salt by-product is easily removed by aqueous extraction. A reliable and versatile synthesis of a stilbene derivative, 2,2-aryl-substituted cinnamic acid esters, using the Wittig reaction was reported [34–36] (Figure 1.3).

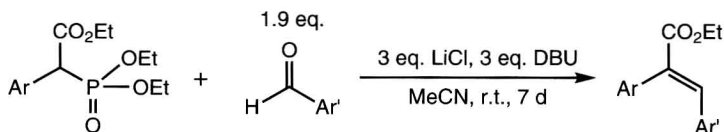


Figure 1.3 Scheme of synthesis of 2,2-aryl-substituted cinnamic acid esters. (Reproduced with permission from Ref. [36].)