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SYNTHESIS OF WARFARIN AS AN ANTICOAGULANT AGENT

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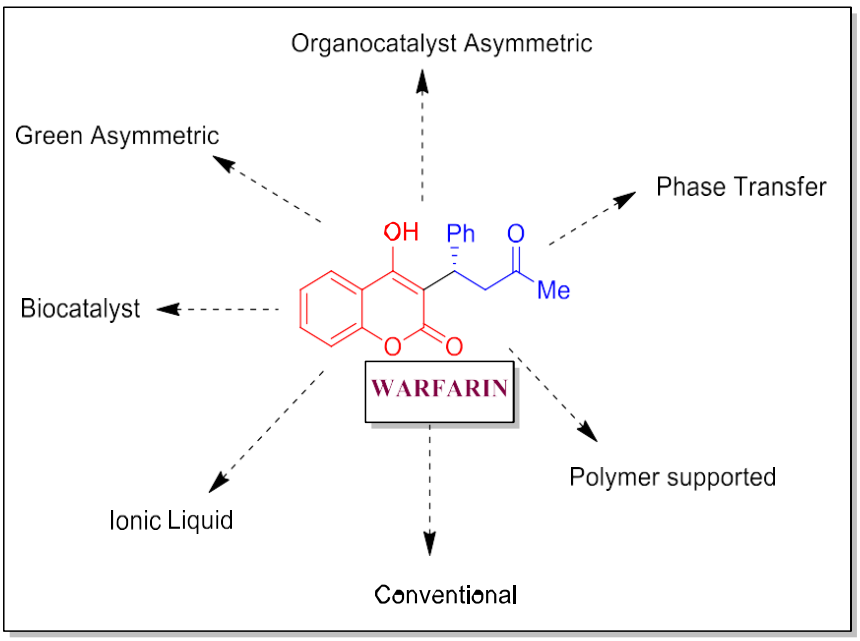
ABSTRACT: This review is a compilation of all the methods used in the synthesis of warfarin. 4-hydroxycoumarin are class of compounds with a wide variety of biological activities, which have found their application in medicine, pharmacological and physiological activities. Warfarin plays an important role in anticoagulants. Synthesis of warfarin through Michael addition condensation has been successfully performed using different methods including the application of ionic liquid, organocatalyst, chiral catalyst, biocatalyst, and polymer-supported catalyst. It covers a literature search over the period from 1944-2020. The importance of this work is its comprehensive literature survey on a specific compound that is warfarin, and those researchers working on warfarin synthesis can find very useful information on the synthetic approaches to their synthesis.

KEYWORDS: Warfarin, anticoagulant, asymmetric, organocatalyst, enatiomeric excess *(ee).*

INTRODUCTION

3-substituted 4-hydroxycoumarins, specifically the 3-(alpha-Acetonylbenzyl)-4-hydroxycoumarin drug known as warfarin. According to systemic biological research among numerous coumarin compounds, 4-hydroxycoumarin derivatives with relatively large, low-polar, and low-hydrophilic substituents in the 3-position are more effective. Every year, around 1- 3 lakh individuals in the United States and 5 lakh in Europe die because of venous thrombosis (blood clotting inside a blood vessel). Anticoagulant warfarin has been considered a drug of choice to treat diseases related to blood coagulation in humans and animals, such as thromboembolism, pulmonary embolism (blood clot in the lungs), atrial fibrillation (abnormal heartbeat), congestive heart failure, deep vein thrombosis (blood clot in the leg), and hip or knee replacement surgery as well as inhibitors of anticlotting protein-C and protein-S. As a result, it has been commercialized and is in high demand all over the world. These compounds are also used as rodenticides to safeguard agricultural goods due to their blood- thinning characteristics [i].



The two main building elements for almost all warfarin formulations are benzylideneacetone and 4-hydroxycoumarin [ii, iii]. Warfarin is one of the derivative of 4-hydroxycoumarin, in which the benzene ring is condensed with a 4-hydroxy pyrone ring in a heterocyclic molecule with a benzopyrone structure. Because of their biological features and remarkable conjugated molecular architecture, 4-hydroxycoumarins (2H-1-benzopyran-2-ones) have attracted the curiosity of many researchers [iv]. Many of them have significant pharmacological qualities, such as analgesic [v], anti-arthritic [vi], anti-inflammatory [vii], anti-pyretic [viii], anti-bacterial [ix], anti-viral [x], and anti- cancer [xi]. 4-Hydroxycoumarin and its derivatives have been employed successfully as anticoagulants in the treatment of disorders that include excessive or unwanted clotting, such as thrombophlebitis [xii], pulmonary embolism [xiii], cardiac conditions [xiv], and antithrombotic drugs [xv]. A number of comparative pharmacological studies of 4-hydroxycoumarin derivatives have revealed strong anticoagulant potency with little side effects and toxicity [xvi]. Warfarin is a 4-hydroxycoumarin-based first generation anti-coagulants rodenticides (FGARs) [xvii], were developed and introduced as rodenticides in the 1940s [xviii]. Which is Vitamin K antagonist that functions by inhibiting Vitamin K epoxide reductase and reducing the Vitamin K-dependent synthesis of blood-clotting proteins [xix, xx]. Since the 1960s it is one of the most commonly prescribed anticoagulants for the prevention of thrombosis [xxi-xxiii].

Warfarin [4-hydroxy-3-(l-phenyl-3-oxobutyl)-2H-l-benzopyran-2-one] is an oral anticoagulant that has been widely used in the treatment of pathological conditions such as thrombophlebitis and myocardial infarction [xxiv, xxv]. It also showed biological activities such as anti-arthritis [xxvi], anti- inflammatory [xxvii], and anti-cancer [xxviii]. Recently, has been utilized as a probe to examine the multiplicity and catalytic activity of microsomal and purified cytochrome P-450 preparations [xxix-xxxiii]. Because of the clinical and pharmacological significance of warfarin and its metabolites, considerable effort has been devoted to developing analytical methods to quantify both warfarin and its metabolites from biological matrices [xxxiv-xxxvii]. Warfarin one of the most effective anticoagulants [xxxviii], has been approved for clinical use as a racemate (warfarin, jantoven, uniwarfin, coumadin, marevan). However, the action and metabolism of the two enantiomeric forms differ. The (S)-form is more active than its mirror version [xxxix-xli]. The chemical synthesis and study of tautomerism [xlii], along with its chemical properties and a wide variety of

biological activities of warfarin have been reported in many papers. Various organocatalysts with primary amines, amino acid functionalities, and natural chiral amines and diamines produced from cinchona have been reported to enhance the asymmetric synthesis of one of the enantiomers [xliii-xlvi]. This review aims to summarize a variety of synthetic approaches to warfarin.

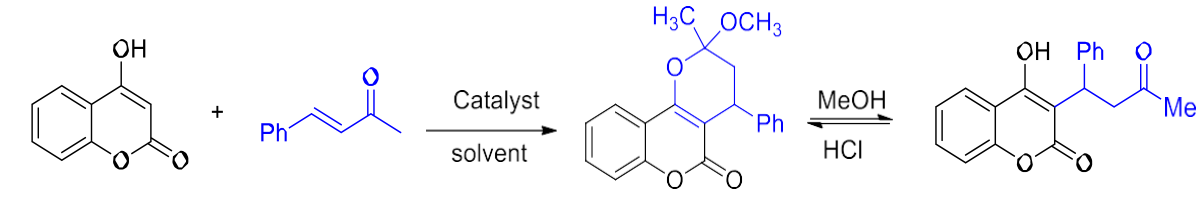
HISTORY

Cattle in North Dakota and Canada began to die unexpectedly in 1921 after suffering from acute internal bleeding [xlvii]. Farmers had converted from corn to sweet clover hay species Melilotus Alba and Melilotus officinalis as cattle fodder [xlviii]. Molds are susceptible to these species if they are stored in dump conditions. The spoiling process can convert the plants natural coumarins into dicumarol, which has anticoagulant effects [xlix]. The sickness was found in cattle that ate spoiled sweet clover, as stated by veterinarians Frank Schofield and Lee Roderick [l]. Karl Paul Link discovered the culprit molecule, dicoumarol, in the 1930s, and warfarin was first employed as a rodenticide in the 1940s [li]. Warfarin was introduced as an anticoagulant in the 1940s and was authorized for use as an anticoagulant in the United State in 1954 after further research [xlviii]. Notably, President Dwight Eisenhower was treated with warfarin for a myocardial infarction (MI) in 1955, after which it became a household name and became more extensively used in the 1960s [xlvii].

SYNTHESIS

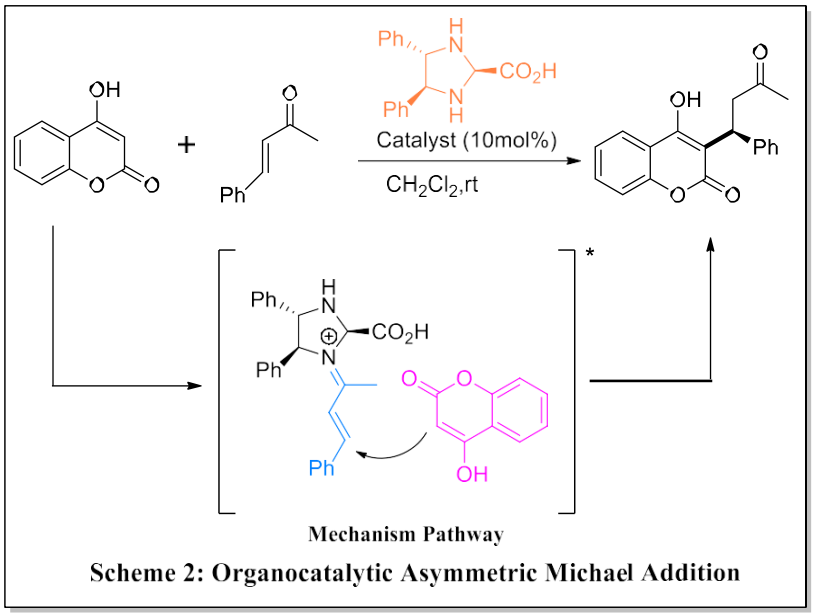
In 1944, Karlpaullink *et al.* carried out condensation of benzalacetone with 4-hydroxycoumarin in ethanol under normal conditions with sodium ethylate, hydrochloric acid, or piperidine as a catalyst yields a mixture of compounds, which contains the typical condensation product as well as the cyclic ketal produced via the ethanol reaction (Scheme 1). The condensation of benzalacetone with 4-hydroxycoumarin can also be achieved without the use of a catalyst by refluxing the two components with water [lii].

1950, Martinseidm, link *et al.* reported a conventional method to synthesize warfarin, where 4- hydroxycoumarin condensed with benzalacetone in the presence of dioxane and piperidine as catalytic amount [liii] [liv]. In



Scheme 1: Synthesis of Warfarin

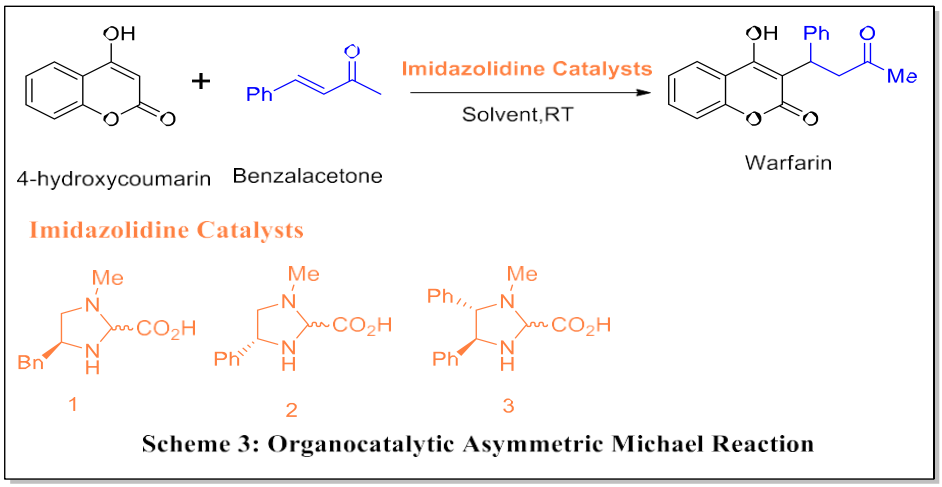
1983, Ernie bush *et al.* reported the synthesis of warfarin and its cyclocoumarol in high yield in which, a suitable 4-hydroxycoumarin was stirred with benzalacetone in refluxing methanol,



Scheme 2: Organocatalytic Asymmetric Michael Addition

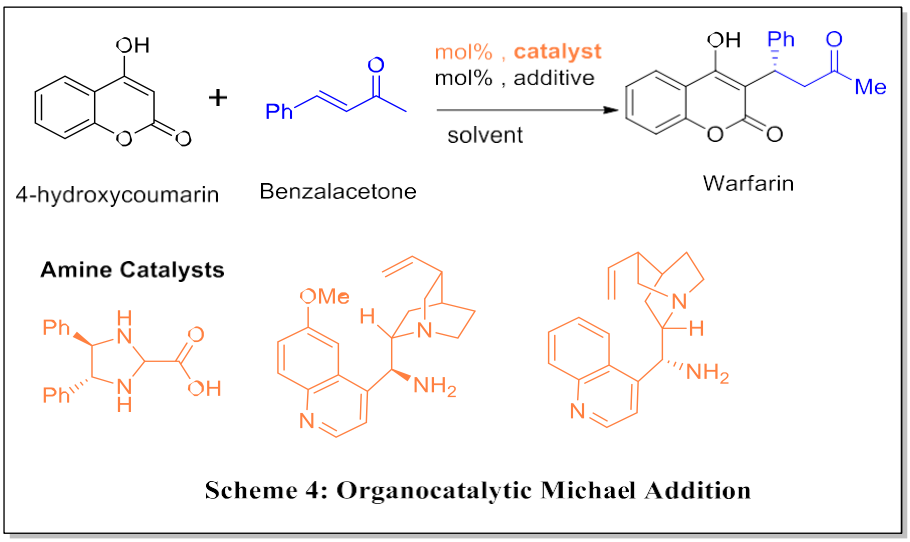
followed by acid hydrolysis, extraction and acidification, in between reaction monitored by thin layer chromatography [lv]. In 1990, Ivo C. Ivanov and a coworker performed a condensation reaction of 4-hydroxycoumarin and benzalacetone in an aqueous medium either alkali fluorides (KF, NaF) or quarternary ammonium salts (Phase-transfer catalysts) [lvi]. Asymmetric organocatalysis methods used to synthesize 4-hydroxycoumarin derivatives such as warfarin were reported in 2003. As optically active medications become more significant in the treatment of patients diseases, more enantiopure drugs become available to the market, either as novel drugs or as the consequence of a racemic switch and that goal is possible by asymmetric catalysis that achieves optically active compound from simple and easily available starting material and catalyst. Synthesis of optically active molecules that have important biological and pharmaceutical activities [lvii]. Jorgensen and colleagues established the first organocatalytic asymmetric Michael addition of cyclic 1,3dicarbonyl compounds, including 4- hydroxycoumarins to, unsaturated enones using (4S,5S)-4,5-diphenylimidazolidine-2-carboxylic acid and obtained good enantiomeric excess *(ee)*. They reported the asymmetric synthesis and also highlighted the proposed mechanism pathway (Scheme 2) [lvii] [lviii].

Further Nis halland *et al.* reported discovery of a new organocatalytic enantioselective process, a simple, effective, and atom-efficient synthesis of optically active warfarin from 4-hydroxycoumarin and benzylideneacetone in the presence of imidazolidine catalysts (Scheme 3). Some screening outcomes for the reaction and they discussed enantiomeric excess and yield of an optically active compound with respect to different imidazolidine catalysts [lvii, lix]. Imidazolidine catalysts would be effective addition catalysts for coumarin compounds to α, β -unsaturated carbonyl compounds [lx]. To concern about environmental contamination, more efforts have been made to develop organocatalysts for asymmetric synthesis in pure water [lxi].

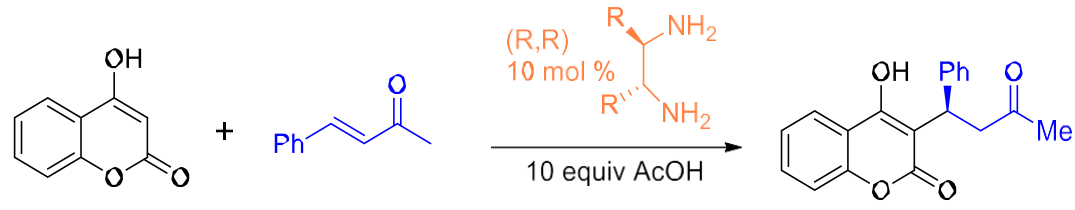


Scheme 3: Organocatalytic Asymmetric Michael Reaction

In 2003, Ilia manolov reported a conventional method to synthesize warfarin, where 4-hydrocoumarin and benzalacetone were mixed and refluxed in water as solvent [lxii]. Preparation of warfarin carried out using a catalyst such as N, N-diphenylurea, urea, aluminium silicate- Polyaniline, magnetic nanoparticle- Polyaniline in the aqueous medium were catalyst was recovered by filtration and heavy gummy mass was formed which then purified [i]. Jian-wu xie *et al.* demonstrated in 2006, highly enantioselective Michael addition of 4-hydroxycoumarin to α, β-unsaturated ketones to be catalyzed by an organic primary amine derived from quinine. In which screening studies of this organocatalytic michael addition were carried out by using derivatives of quinine catalyst, solvent, acid additives, and so on, and discussed with yield, enantiomeric excess (Scheme 4) [lxiii]. In 2006 Hyunwoo kim *et. al.* prepared and investigated chiral vicinal diamine-catalyzed synthesis of warfarin were further screened by using different catalysts and the effect of acetic acid. They also proposed a mechanism of vicinal diamine-catalyzed synthesis of warfarin (Scheme 5) [lxiv] [lxv].



Scheme 4: Organocatalytic Michael Addition



4-hydroxycoumarin Benzylideneacetone (R)-Warfarin

Where R= $(CH_2)_4$, Phenyl, 2-tolyl, 1-naphthyl

Scheme 5: Synthesis of Optically active Warfarin

In 2009, Kristensen *et al.* performed fully synthesized phenyl glycine-derived primary amine organocatalysts for the one-step synthesis of optically active warfarin, an essential anticoagulant, in which they studied asymmetric organocatalytic preparation of warfarin, and report efficiency of new phenyl glycine-derived organocatalysts than primary amine organocatalysts [lxvi]. They tried amine, amine alcohol, and silyl ether in preparation for warfarin with co-catalyst. Some of them show in Figure 1

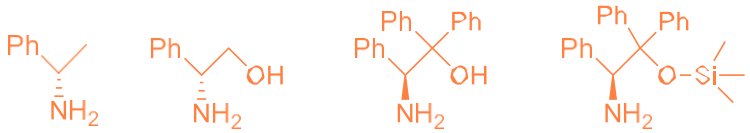
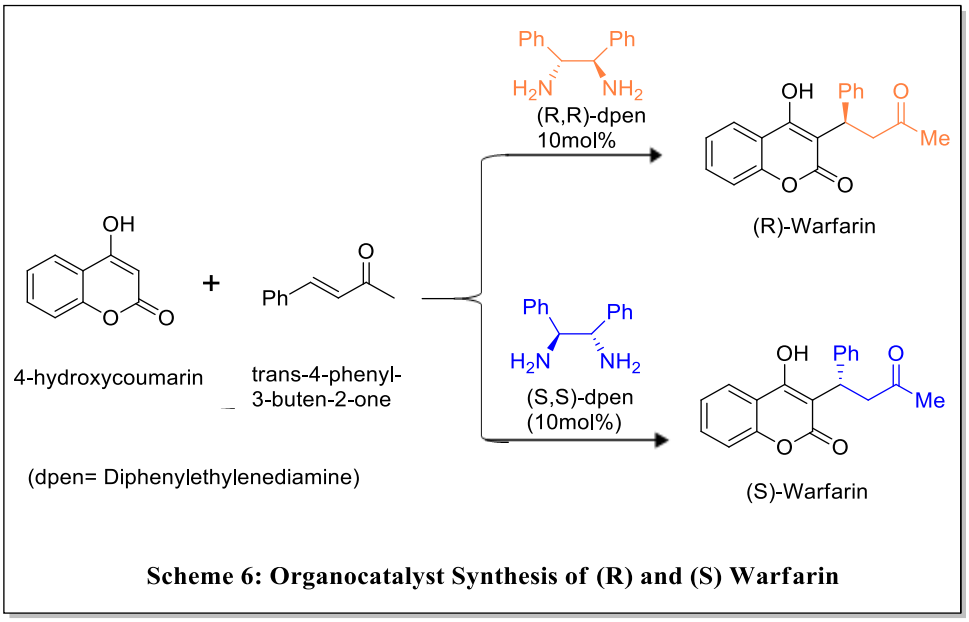


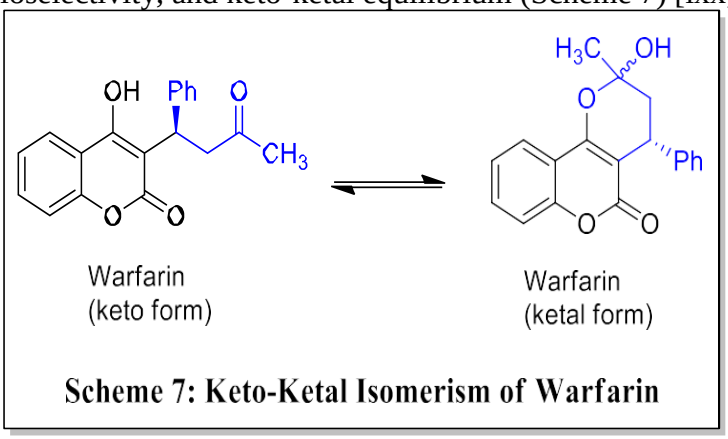
Figure 1: Primary Amine Organocatalysts for Warfarin Synthesis

In 2009, Zhenhua dong and coworker performed the asymmetric Michael addition of 4-hydroxycoumarin to α, β -unsaturated ketones in the presence of C2-symmetric secondary amine amide catalyst such as (L)-Proline derivative, (L)-piperidine-2-carboxylic acid derivative and (L)-phenyl glycine derivative [lxvii]. A series of catalysts, additives, and solvent screened showed a significant effect on the rate, yield and enantioselectivity. In 2010 Terence *et al.* recently reported a simple one-step green synthesis of warfarin using a chiral organocatalyst. They also proposed a model for stereoinduction in the synthesis of warfarin (Scheme 6), which was directly purified by column chromatography or mixed solvent recrystallization [lxviii] [lxix].



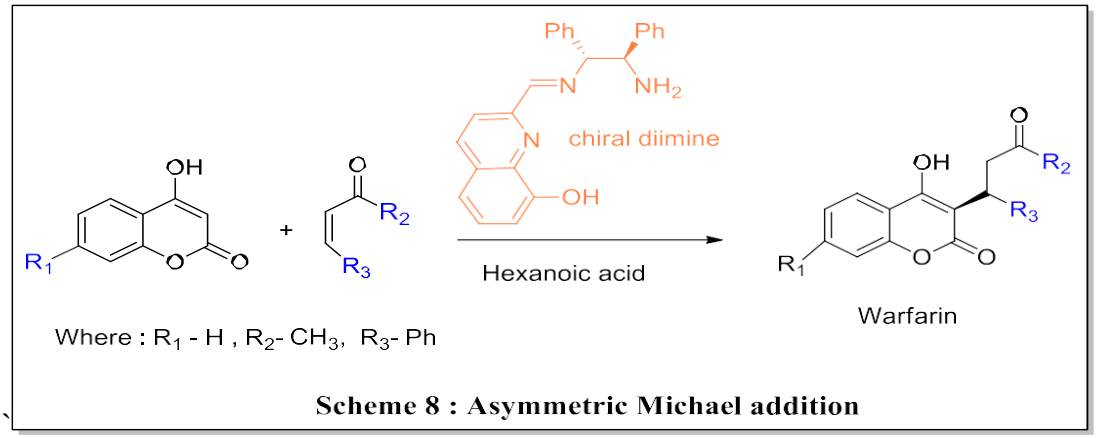
Scheme 6: Organocatalyst Synthesis of (R) and (S) Warfarin

The mechanistic details are rich, incorporating biologically relevant concepts such as imine-iminium formation, keto-enol tautomerism, Michael addition, enamine hydrolysis, organocatalysis, enantioselectivity, and keto-ketal equilibrium (Scheme 7) [lxx].



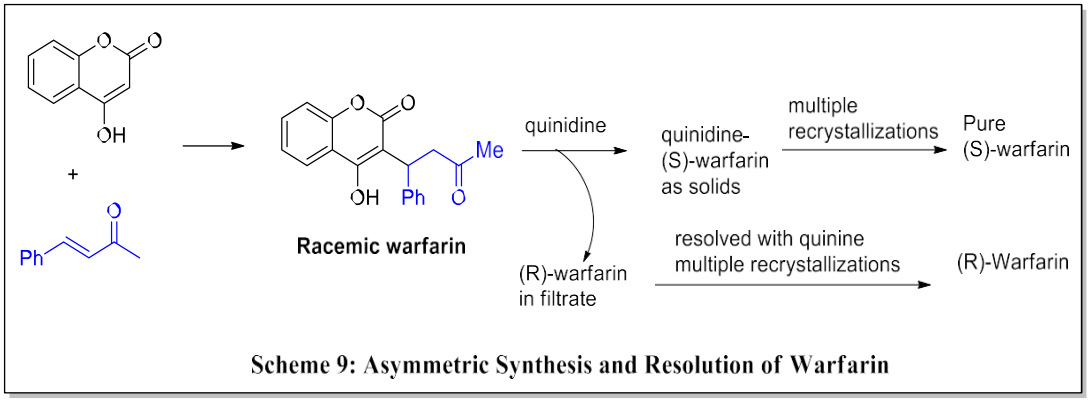
Scheme 7: Keto-Ketal Isomerism of Warfarin

In 2011 Xi zhu *et al.* carried the asymmetric Michael addition of 4-hydroxycoumarin and unsaturated ketone, an in-situ generated primary amine-imine organocatalyst was produced (Scheme 8) [lxxi].



Scheme 8 : Asymmetric Michael addition

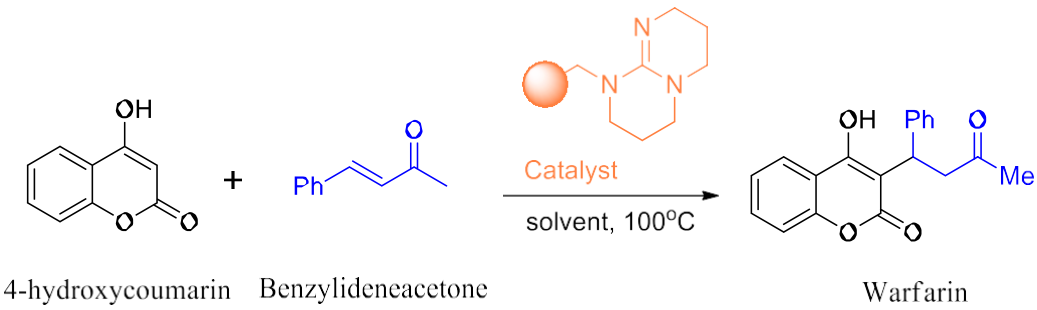
In 2012 JJ Song *et al.* reported the chemical resolution of a single enantiomer of warfarin from a racemic mixture. Where racemic mixture was treated with quinidine to form diastereomeric salt that separated on crystallization (Scheme 9) [lxxii].



Scheme 9: Asymmetric Synthesis and Resolution of Warfarin

In the year of 2012, Bang-Hua xie *et al.* reported enzyme-catalyzed Michael addition of 4-hydroxycoumarin and benzalacetone in which lipase from porcine pancreas (PPL) was used as a biocatalyst in the organic medium in the presence of water to synthesize warfarin, were the effect of reaction conditions such as solvents, temperature, and substrate molar ratios was thoroughly examined. In solution, the Michael addition products were discovered to be in fast equilibrium with a pseudo diastereomeric hemiketal form. They utilize inexpensive regenerable resources, and biocatalytic processes have been proven to be more economically feasible environmentally beneficial, also sustainable than existing chemical methods [lxxiii-lxxv]. In 2013, Tao Shi and co- workers published an atom-economic synthesis of optically active warfarin using a chiral Metal- Organic Framework (MOF) organocatalyst. They developed a chiral metal-organic framework (MOF) organocatalyst by post-synthetically modifying [lxxvi] MIL-101 and the chiral primary diamine (1R, 2R)-1, 2-diphenyl ethylenediamine. MOFs were used in heterogeneous catalysis, and chiral heterogeneous catalysts were used in the asymmetric synthesis of (S)-warfarin with high enantioselectivity and yield. Diamine is coordinated to MIL101's open metal coordination site chromium (III).

The chiral organic ligands (1R, 2R)-1, 2-cyclohexane diamine [(1R, 2R)-CHDN] and (1R, 2R)-1, 2-diphenyl ethylenediamine [(1R, 2R)-DPEN] were chosen as the chiral MIL- 101-based catalysts CDMIL-1, CDMIL-2, CDMIL-3, and CDMIL-4 [lxxvii]. They performed the Michael addition between 4-hydroxycoumarin and benzylideneacetone were solvent such as THF, toluene, chloroform in presence of chiral organic ligand also compared studies of yield and enatiomeric excess (*ee).* In 2013, Matteo alonzi *et al.* reported synthesis of novel polystyrene- supported TBD catalysts and their used in synthesized of warfarin were polystyrene-bound 1, 5, 7-triazabicyclo [4.4.0] dec-5-ene (TBD) has been prepared and the catalyst was recovered just by filtration (Scheme 10) [lxxviii]. PS-TBD is a polymer-supported organocatalyst consisting of a covalently attached guanidinic TBD moiety to polystyrene that has been employed successfully in a variety of processes [lxxix-lxxxiii].



4-hydroxycoumarin Benzylideneacetone Warfarin

Scheme 10: Synthesis of Warfarin by Polymer-Supported Organocatalyst

In 2014, Maria Rogozin´ *et al.* reported green chemistry type asymmetric synthesis of warfarin on water with or without organic co-solvent catalyzed by organic primary amines and also discussed the application of enantiomerically pure (S, S)-diphenyl ethylenediamine to

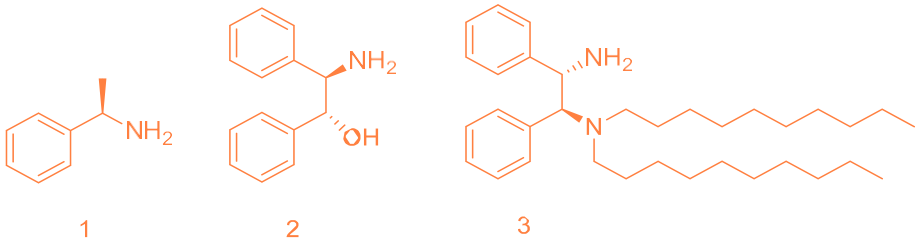


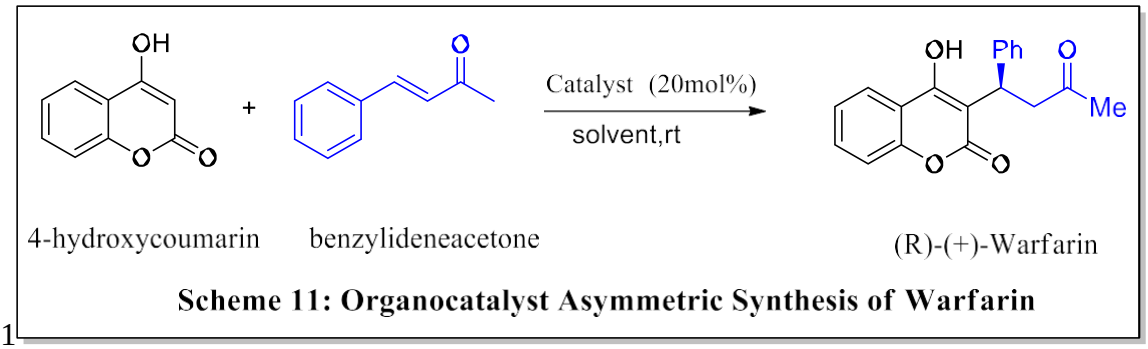
Figure 2: Chiral primary amine tested in Michael reaction

achieve pharmaceutically active compounds in better yield with good enantioselectivities via reaction carried by ultrasound. They discussed reaction screening with different chiral primary amines and also evaluated solvent effect, temperature, time and enatiomeric excess *(ee).* The influence of acid additives and catalyst loading on reaction enantioselectivity was studied further to improve it. The reaction was examined using several primary amine organocatalysts, some of which were easily accessible and some of which were synthesized by a series of hydrophobic amines fitted with an alkyl chain for reactions carried out in an aqueous environment, in which few are represented in figure 2 [lxxxiv, lxxxv].

In the year of 2016, Aazam Monfared and coworkers reported the synthesis of anticoagulant racemic warfarin using 4-hydroxycoumarin and benzalacetone in the presence of an ionic-liquid catalyst such as imidazolium-based ionic liquids [bmim] BF4 and [bmim] Br and other reaction solvents such as H_2O, pyridine and ammonia. They demonstrate the potential of ionic liquids in the development of green methods for the production of the C-C bond via reaction condensations without the need for catalysts or organic solvents. The work-up procedures were quite straightforward, and the products do not require further purification. They also studied Michael addition for the synthesis of warfarin and its ring-closing derivatives [lxxxvi].

Organocatalysts for application to the enantioselective synthesis of warfarin were developed by Murat ısık *et al.* in 2016. They experimented with a new chiral sec-amine/amidine-base hybrid catalyst, 2-aminoDMAP/prolinamide, and found that they could catalyze conjugate addition of 4- hydroxycoumarin and different benzylideneacetone with good yield and enantioselectivities (Scheme 11). They monitored the reaction using different 2-amino base

organocatalysts with various solvents (Figure 3). Further, they modified a 2-amino base organocatalyst to synthesize diastereomeric pair of 2-aminoDMAP/ prolinamides (R, R, L) and (S, S, L) for refocused on conjugation addition for reaction parameter optimization, with some solvent were tested. They believed that the reaction necessitates the use of either a primary or secondary amine catalyst to activate these mutually unreactive partners, however alone it's insufficient to achieve appropriate enantioselectivity and yield [lxxxvii].



Scheme 11: Organocatalyst Asymmetric Synthesis of Warfarin

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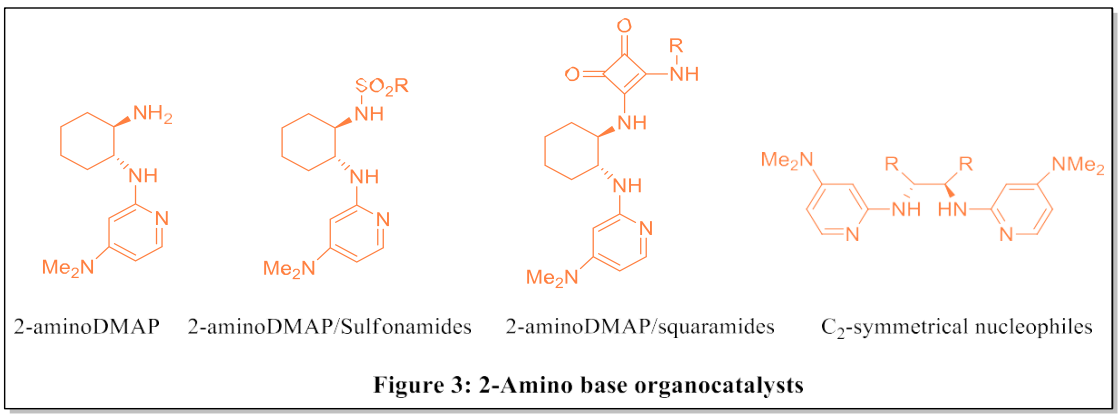
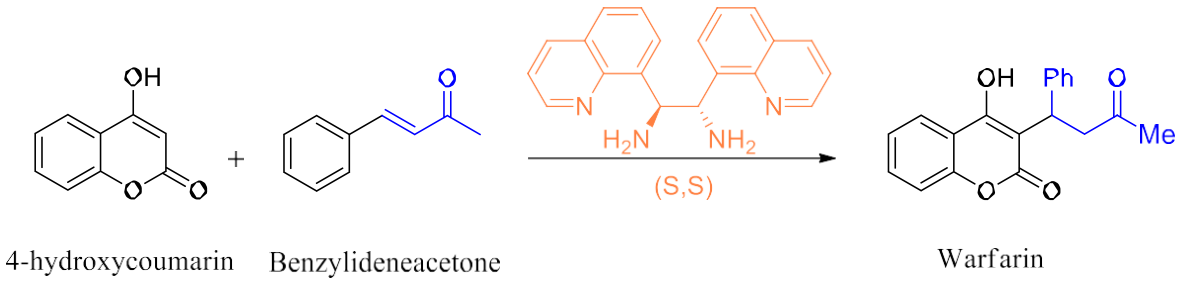


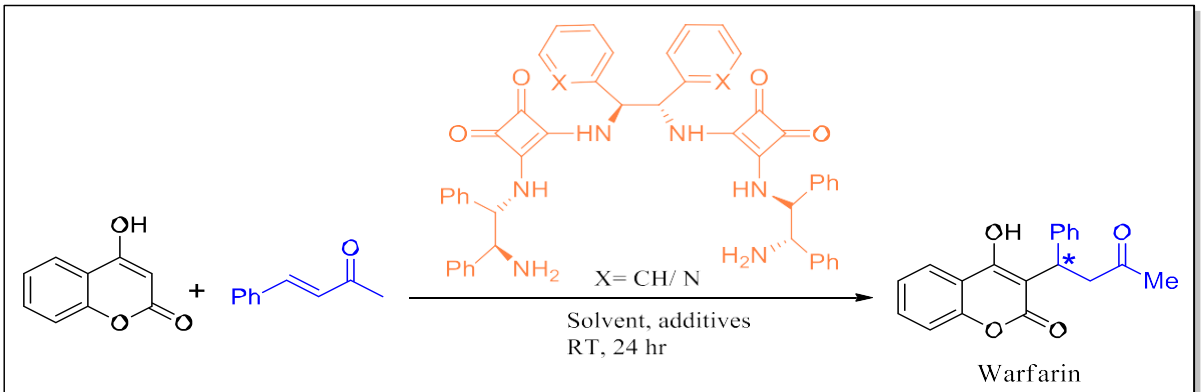
Figure 3: 2-Amino base organocatalysts

In 2016, Alexander Kucherenko *et al.* reported green synthesis of both enantiomers of the anticoagulant Warfarin in an aqueous medium was achieved using an asymmetric iminium-type Michael reaction with catalysts and acid additives. Through stereospecific diaza-Cope rearrangement with 2, 2'-(1, 2-diaminoethane-1, 2-diyl) diphenol (HPEN) a novel enantiomerically pure C_2-symmetric quinoline (isoquinoline) derived 1, 2-diamines were synthesised from corresponding aldehydes (Scheme 12). They also investigated the (S, S) catalyzed Michael addition reaction in the presence of acidic additives, specifically acetic, tartaric (TA), or mandelic (MA) acids. Further to improve the reaction conditions acid additives and the catalysts was used and comparable studies of yield, enantiomeric excess were carried out. In the asymmetric Michael reaction between 4-hydroxycoumarin and an unsaturated ketone, they also investigated the catalytic performance of synthesized quinoline-derived diamines and for comparison with known trans-1, 2-diamines bearing the pyridine and naphthalene structural fragments [lxxxviii-xci].



Scheme 12: Asymmetric Synthesis of Warfarin

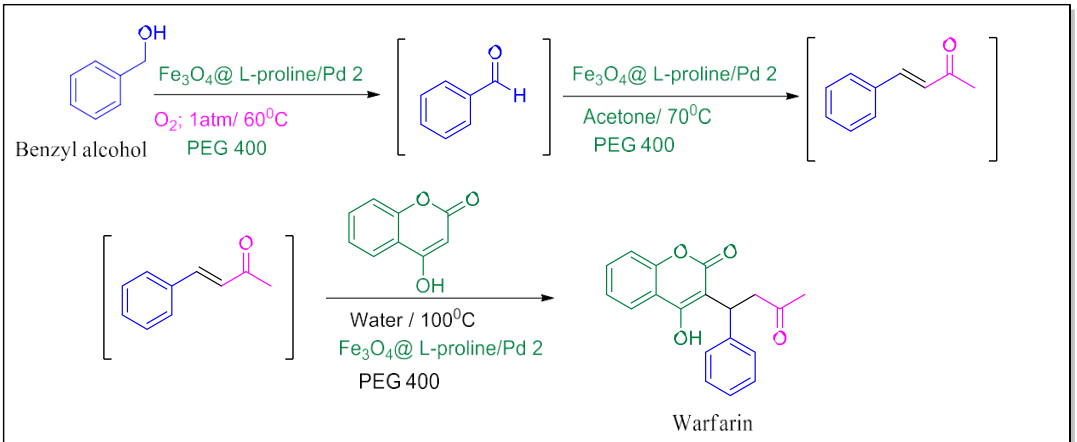
Warfarin was developed through the Michael addition of 4-hydroxycoumarin to benzalacetone under a variety of acid- or base-catalyzed conditions [xcii]. In 2016, Kochetkov *et al.* reported novel C2-symmetric N, N'-bis(2-amino-1,2-diphenylethyl) squaramides with 1,2-diphenylethane and 1,2-diphenylethane spacer groups were developed and used as organocatalysts in asymmetric additions of 4-hydroxycoumarin to α, β-unsaturated ketone (Scheme 13) [xciii]. The proposed catalysts recyclability and synthetic usefulness for the asymmetric synthesis of prospective chiral medications via acylation reactions were demonstrated .Yield and enantiomeric enrichment were higher with pyridine-containing catalysts than with diamines with the 1,2-diphenylethane-1,2- diamine linker group [xciii], it is also synthesized in the presence of catalyst 9-amino-9- deoxyepiquinine TFA salt [xciv], primary amine thiourea catalyst [xcv], Primary amine phosphinamide bifunctional catalyst [xcvi], 8-quinoline fragments along with mandelic acid have recently been found to be the preferred catalyst for the asymmetric synthesis of warfarin in pure water [xcvii].



Scheme 13: Organocatalyst Asymmetric Synthesis

Recently in 2019, Sanjiv O. Tomer and Hemant P. Soni reported synthesis of racemic warfarin by using Fe3O4@L-Proline/Pd nanocomposite, for that The surface of L-proline capped Fe3O4 nanoparticles (Fe3O4@L-proline NPs) was loaded with metallic palladium. It is one of method to synthesized warfarin from benzyl alcohol by green way (Scheme 14). The Pd on the surface was responsible for the in-situ oxidation of benzyl alcohol and its derivatives to the appropriate aldehyde. Because of the presence of the L-proline organocatalyst on the surface of Fe3O4 NPs, this condensed with acetone to generate the aldol condensation product, benzylideneacetone, at 70°C. Later, 4-hydroxycoumarin was added to condense with in situ-produced benzylideneacetone through a Michael addition to yield the target product (±)-warfarin. It was discovered that benzyl alcohol can be transformed into the ultimate

product, (±)-warfarin. They carried out a one-pot conversion of benzyl alcohol and its derivatives to benzylideneacetone in the presence of Fe3O4@L-proline/Pd2 NCs under optimized reaction settings, and by employing a solvent like PEG-400, they made the process truly green [xcviii].



Scheme 14 : Synthesis of (±)-warfarin through 3-way catalysis in the presence of Fe3O4@L-proline/Pd2

Recently in 2020, Jee Seong Kwak *et al.* reported a reconfigurable reaction platform capable of batch, continuous flow, and plug-flow synthesis was used to optimise the asymmetric synthesis of warfarin, an important anticoagulant. Furthermore, this platform has been integrated with a novel, multidimensional, multiple variable analysis tool capable of evaluating multiple critical quality attributes (CQA), in this case percent conversion and enantiomeric excess from a single injection that is repeatedly recycled in a closed loop of chromatography columns, a detector, and a heart-cut valve [xcix].

CONCLUSION

This review summarizes the use of several techniques in warfarin synthesis over the last few years. Asymmetric synthesis allows for the development of new reactions that produce optically active compounds from existing starting materials and catalysts, which is crucial for the treatment of diseases in patients. Also it will be useful in the creation of safe organocatalysts and reagents, on which many researcher worldwide have been working for years. Their utility is becoming clearer by the day, and their prospects for laboratory-scale reactions and industrial applications are promising.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

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