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Diketene

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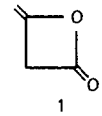
Contents

I. Introduction

Diketene (4-methyleneoxetan-2-one, 1) is a reactive and versatile compound which is used for the introduction of functionalized C_2, C_3, and C_4 units into organic compounds, although it is best known as a reagent for the preparation of acetoacetic acid derivatives.



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Diketene appears to be an ideal compound for chemical study; it is inexpensive, readily available, reactive, and highly functionalized. Furthermore, many aspects of diketene chemistry remain either undeveloped or unexplored.

An examination of the literature that references diketene reveals several salient points. First, this litera-

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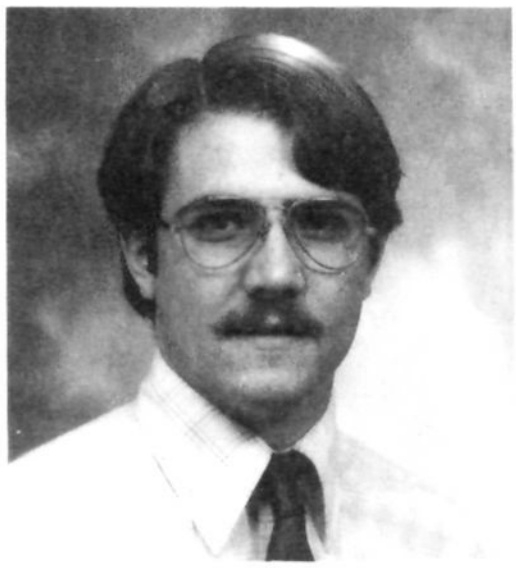


Robert Clemens received his undergraduate education at Ursinus College, worked briefly in the polymer industry, and then completed his doctorate at Princeton University. In 1982, Bob joined the Eastman Chemicals Division Research Laboratories, where he spends much of his time exploring new synthetic applications of diketene and its derivatives, thereby continuing his interest in highly functionalized, small-ring heterocycles.

ture is both fragmented and diverse, with large portions of innovative diketene research documented only in incomplete communications, obscure journals, or patents. Secondly, the chemistry of diketene is inseparably intertwined with that of other acetoacetic acid derivatives, and a chemical understanding of these latter derivatives is essential for the appreciation of diketene chemistry. Finally, there is relatively little synthetic methodology based upon diketene, in spite of some notable successes (vide infra) in this regard.

This review was written in response to the aforementioned points. Thus, a major purpose of this text is to catalog every type of synthetic transformation that has been effected with diketene and to provide a comprehensive guide to the literature written from 1907 through early 1985 which describes this chemistry. A realistic presentation of the patent literature, which was requisite to a thorough review, precluded the tabulation of the specific substrates on which a given reaction was actually run. The reactions shown in the diagrams have therefore been selected as representative examples for which experimental details were provided; the original literature should be examined for information regarding other substrates that were used. If available, a U.S. equivalent has been listed for foreign patent references; *Chemical Abstracts* citations are provided for references that may not be easily accessible.

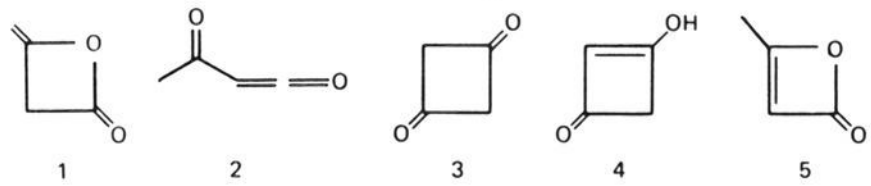
The first three sections of this review provide an historical perspective on diketene chemistry, an overview of several fundamental diketene reactions, and a discussion of acetoacetylation and some nonheterocyclic applications of acetoacetate derivatives. Heterocyclic chemistry which is based on diketene is discussed in sections IV and V, and the final section describes various other aspects of diketene chemistry.

Throughout this review, liberal digression has been made into the chemistry and utility of acetoacetic acid derivatives. The advantages derived from obtaining a better insight into the synthetic applications of diketene will hopefully outweigh the disadvantages of a more fragmented review.

In 1940, Boese first reviewed diketene chemistry,[1] and an excellent overview of both ketene and diketene chemistry appeared in 1968.[2] More recently, Kato has reviewed some uses of diketene in heterocyclic synthesis,[3] general review articles have been published in Russian,[4] Japanese,[5] and Polish,[6] and several brief sections of diketene chemistry have appeared in books.[7]

A. Historical–Structure Elucidation

The elucidation of the structure of diketene (which required 45 years) provides an interesting insight into diketene chemistry and into the difficulties associated with structure determination in the absence of modern spectral techniques. An understanding of this structure determination is a prerequisite to comprehending pre-1950 papers on diketene chemistry, as no less than five structures (**1**–**5**) were seriously considered.



1 **2** **3** **4** **5**

In 1907, Wilsmore prepared ketene by immersing a glowing platinum wire into acetic anhydride and then collecting the resulting gaseous byproducts at low temperature. He noted that ketene dimerized exothermically upon warming to provide a lachrymatory, brown liquid,[8] and distillation of this crude material at reduced pressure afforded the first pure sample of the ketene dimer.[9] Wilsmore further noted that this ketene dimer reacted with water to form acetoacetic acid, which subsequently decomposed into carbon dioxide and acetone (Scheme I). The ketene dimer also readily reacted with aniline to form acetoacetanilide, with sodium ethoxide to afford sodium ethyl acetoacetate (**6**), and provided dehydroacetic acid (**7**) when exposed to pyridine. On the basis of his early experiments, Wilsmore proposed the acetylketene structure (**2**) for the ketene dimer.

Shortly thereafter, Staudinger demonstrated that the dimers (e.g., **8**) of several substituted ketenes were undoubtedly 1,3-cyclobutanediones.[10] These latter dimers reacted quite differently with aniline than did the ketene dimer and produced acetanilides (e.g., **9**) (Scheme II). Nonetheless, Staudinger suggested that Wilsmore's ketene dimer was 1,3-cyclobutanedione in its monoenolic form (**4**).

Wilsmore reasoned that the product (**10** or **11**) which resulted from bromination of the ketene dimer would

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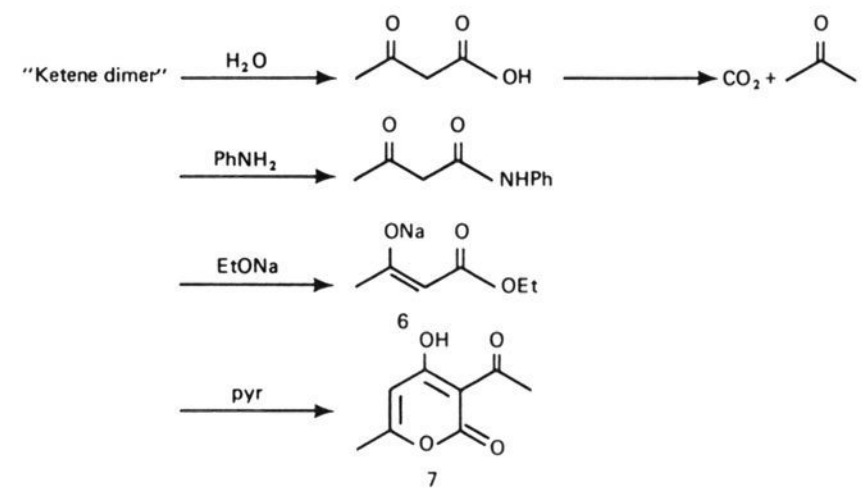

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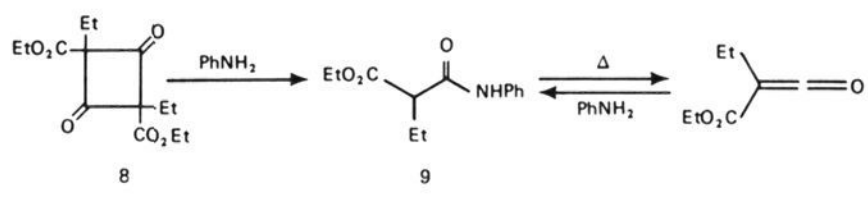

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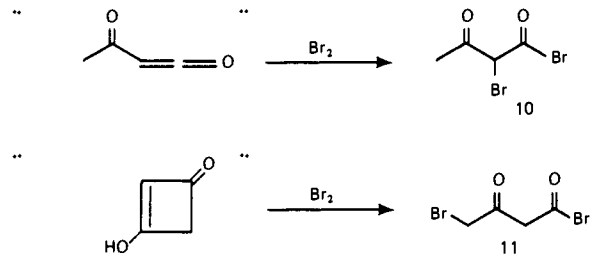
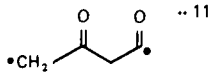


differentiate the two proposed structures **2** and **4**[11] (Scheme III).

The product, 4-bromoacetoacetyl bromide (**11**), appeared to support Staudinger's cyclobutanedione structure, but Wilsmore still had difficulty rationalizing the facile, room-temperature conversion of the ketene dimer into dehydroacetic acid (**7**). Also, the ketene dimer reacted with alcohols under acidic catalysis to give acetoacetate esters, while acetate esters were formed from other cyclobutanediones. Wilsmore noted that the ketene dimer "behaves as if the ring were not completely closed, that is to say, as if its constitution were



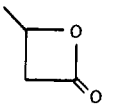
A subsequent, detailed study of the chemistry of 2,4-dimethyl-1,3-cyclobutanedione suggested that it was highly unlikely that the ketene dimer was a cyclobutanedione because of the following: (1) all other cyclobutanediones were crystalline solids, while the ketene dimer was not; (2) all other cyclobutanediones formed simple carbonyl derivatives, while the ketene dimer did not; (3) no other cyclobutanedione reacted with alkoxides to form acetoacetic esters.[12]

The debate continued as to which of the (incorrect) structures (**2**, **3**, or **4**) was appropriate for the ketene dimer, but no new structures were suggested.

During the ensuing 20 years (1916–1936), diketene found considerable use in the preparation of a variety of acetoacetates and derivatives thereof, but there were no further developments regarding structure determination. In 1936, Hurd reported that ozonolysis of the ketene dimer provided pyruvaldehyde, "identified" as its osazone derivative, and acetic acid.[13] He therefore suggested a β-crotonolactone structure (**5**) for the ketene dimer, and he further suggested the possibility of an equilibrium between the acetylketene and β-crotonolactone. Although the structures **2** and **5** were inconsistent with Wilsmore's bromination experiment, the formation of 4-bromoacetoacetates could be rationalized via the known isomerization of 2-bromoacetoacetates into the corresponding 4-isomers. Unfortunately, Hurd and co-workers had identified formaldehyde phenylhydrazone (mp 144–145 °C) as the pyruvaldehyde osazone (mp 143–144 °C),[13] an error which was not to be recognized for almost 14 years. It should be respectfully noted, however, that Hurd and co-workers made many invaluable contributions to early diketene chemistry in their search for the correct structure of the ketene dimer.

Further complicating structure determination was the failure to isolate ketene or any other gases upon pyrolysis of the ketene dimer.[14] In retrospect, this failure was largely due to inappropriate trapping conditions, and the conversion of diketene into ketene was eventually found to be quite efficient (see section IIA).

By 1940, Boese reviewed both the aforementioned structural controversy and the industrial applications of diketene.[1] In his review, Boese reported that the ketene dimer afforded β-butyrolactone (**12**) upon hydrogenation, and he credited A. L. Wilson with suggesting 4-methylene-2-oxetanone (**1**) to be the correct structure of the ketene dimer.[15]



Hurd noted that while the newly proposed structure (**1**) conveniently explained both the acetoacetate formation and the hydrogenation product **12**, this structure was inconsistent with the formation of dehydroacetic acid. Hurd attempted to refute Wilsmore's earlier bromination experiments by chlorinating the ketene dimer at low temperature, but he isolated only 4-chloroacetoacetyl chloride.[16] Undaunted, Hurd found that diketene reacted with hydrogen chloride to give acetoacetyl chloride, a product which was consistent with an acetylketene structure.[17] Hurd continued as an active proponent of the β-crotonolactone structure, and he assumed that β-crotonolactone (**5**) underwent a facile transformation into acetylketene.[18]

In 1943, Rice and Roberts prepared ketene in excellent yield by pyrolysis of the dimer. They felt that this result was consistent only with the cyclobutanedione structure, because the reaction was not affected by radical inhibitors.[19] These authors did, however, note that the cyclobutanedione structure **3** was inconsistent with the high dipole moment (3.53 D) observed for gaseous diketene.

It was 1950 when Hurd repeated his ozonolysis of diketene, isolated formaldehyde, and accepted the correct methyleneoxetanone structure (**1**),[20] thereby ending an unusually long and arduous structure determination of a simple molecule.

In addition to the chemical reactions that were used to determine the structure of the ketene dimer, a variety of physical measurements were made. Prior to 1940, these measurements included determinations of the molecular weight, the refractive index,[11b] and the ultraviolet spectrum.[18] The dipole moment was measured,[21] and the Raman spectrum was analyzed.[21,22]

An infrared spectrum, first obtained in 1946, established that the ketene dimer contained a four-membered ring,[23] and the structure was unequivocally established in 1952 by X-ray diffraction.[24] This structure (**1**) was later corroborated by an historic 18-MHz ^{1}H NMR study;[25] the NMR spectrum has subsequently been assigned[26] and corrected,[27] and the unusual shift values have been explained.[28] Electron diffraction,[29] microwave spectroscopy,[30] and mass spectrometry[31] studies have also been performed on diketene.

B. Physical Properties

Diketene is a colorless liquid at 25 °C and has a sharp, pungent odor. A pure sample of diketene melts at −7.5 °C and boils at 127 °C (760 mm) with some decomposition. It is immiscible with hexane and only slightly soluble in water but is readily miscible with most organic solvents.

Although diketene is less toxic than ketene,[32] it is a powerful lachrymator. If improperly handled, diketene can cause eye injury or burns to the skin or respiratory tract.

C. Preparation, Storage, and Handling

Diketene is normally prepared by the dimerization of ketene,[33] which in turn is prepared from the pyrolysis of acetic acid, acetic anhydride, or acetone at temperatures near 750 °C. Diketene is most conveniently obtained from a commercial supplier.

Diketene is best shipped and stored as a solid, in which form it can be stored for many months without change. In the liquid state, diketene undergoes gradual discoloration and decomposition. Because diketene can liberate carbon dioxide during its decomposition, it should not be stored in glass bottles. Diketene can be stabilized by the addition of that amount of water sufficient to hydrolyze any residual acetic anhydride present in the crude product.[34] Other stabilizers for diketene include sulfur,[35] certain alcohols and phenols,[36] and a series of borate and sulfate salts.[37] Thus, unstabilized diketene was stored for 1 year at 25 °C and decreased from 95.3% to 38.2% assay, while diketene stabilized with 1% anhydrous copper sulfate was stored under similar conditions and retained a 94.5% assay.[37a] However, no stabilizer is superior to storing diketene in a freezer. The mechanism of stabilization of diketene does not appear to be well understood.

Crude diketene can be purified by high vacuum distillation to provide a high assay material that is acceptable for almost any purpose. Ultrahigh purity diketene (99.99%) has been prepared by low-temperature recrystallization.[38]

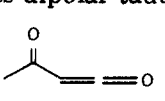
Reactions of diketene are often extremely exothermic, and diketene will rapidly self-condense in the presence of both acidic and basic catalysts. Therefore, it is important that diketene be kept free from contamination during storage, and that provisions be made for adequate cooling when diketene is used in a reaction. Diketene is almost always added portionwise to other reagents to maintain low concentrations of diketene and to facilitate adequate temperature control. Dedicated equipment is generally required for industrial-scale reactions.

D. Uses of Diketene

Diketene has few direct end uses. It is reported to be a potent bactericide which is useful for disinfecting large areas.[39] Also, it can raise the octane number of gasoline 0.6 units at a 0.075% (v/v) loading.[40] In some cationic polymerization reactions, diketene is used as a secondary "catalyst" (activator).

II. Fundamental Reactions of Diketene

Diketene is a strained molecule ($E_{strain} \sim 22.5$ kcal mol^{-1})[41] which is readily ring-opened and therefore frequently appears to react as acetylketene (**2**) or one of its dipolar tautomers (**13** or **14**).



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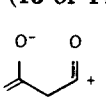

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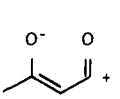

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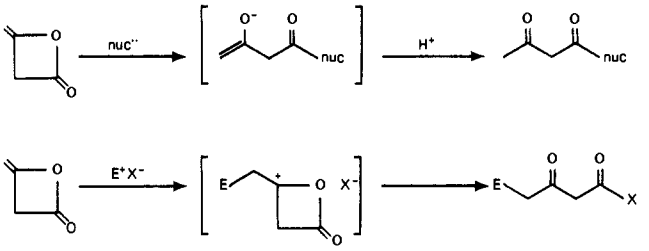
SCHEME IV



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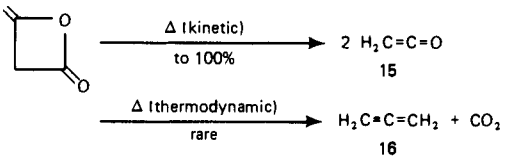


Nucleophilic ring-opening of diketene usually occurs at the acyl carbon–oxygen bond. Electrophiles react with the double bond of diketene, followed by nucleophilic attack at the lactone carbonyl group (Scheme IV). There are also a few diketene reactions in which ring-opening occurs at the vinylic carbon–oxygen bond (see section VI.D) and a series of reactions in which the β-lactone ring remains intact (see section VI.B).

Ring-opening of diketene normally results in the formation of an acetoacetic acid derivative, even if this latter compound is only a transient intermediate which undergoes further reaction. Therefore, this review discusses some acetoacetate chemistry (alkylation, nitrosation, halogenation, etc.), but only as this chemistry is related to diketene. A more deliberate treatment of acetoacetate chemistry can be found in other sources.[42]

A. Pyrolysis

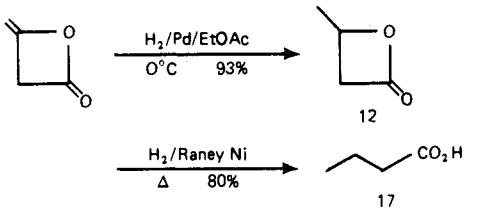
In the gaseous phase (dilute), diketene is thermally stable to temperatures above 400 °C. It can be cracked at higher temperatures to give two molecules of ketene (**15**) in nearly quantitative yield (Scheme V). This pyrolysis can be performed in a "ketene lamp" with a glowing platinum filament, or in a hot tube, and is an excellent method of laboratory-scale ketene preparation.[43]

The pyrolysis of diketene has been carefully studied, since theoretical calculations have shown that the thermodynamically favored pathway for diketene pyrolysis would be the formation of allene (**16**) and carbon dioxide instead of the normally observed ketene.[19] Also, the high-temperature isomerization of diketene into 1,3-cyclobutanedione or 2,4-dimethylene-1,3-dioxetane has been studied via semiempirical SINDO calculations.[44]

The gas-phase pyrolysis of diketene in a quartz tube has been determined to be a homogeneous first-order reaction in which carbon–carbon bond cleavage is the slow step of the reaction. The reaction is under kinetic control, and the activation energy for the conversion of diketene into ketene has been estimated to be 50 kcal mol^{-1}.[45]

The formation of allene during pyrolysis of diketene has been reported on two occasions. Thus, passing diketene over a new nichrome filament gave, in addition to ketene, a 6.5% yield of allene and a 6.5% yield of CO_2.[46] A patent later claimed that a 16.2% yield of

SCHEME VI



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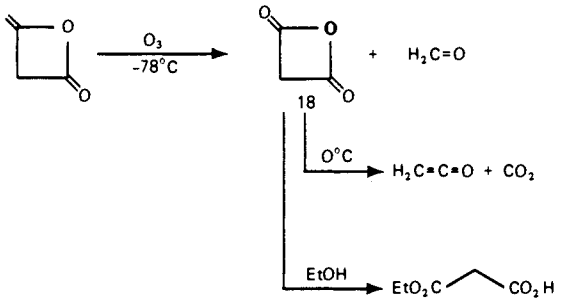


allene had been obtained from the pyrolysis of diketene at 550 °C in a reactor constructed entirely of high-purity copper.[47] It has not yet been determined whether the allene is formed directly from diketene or is formed from the reaction of ketene and the methylene which results from further pyrolytic decomposition of ketene.

B. Hydrogenation

Diketene can be selectively hydrogenated to provide either β-butyrolactone (12) or butyric acid (17) (Scheme VI).

Early attempts to hydrogenate diketene at 25–100 °C with palladium catalysts led to mixtures of 12 and 17,[48] but pure β-butyrolactone was later obtained by performing the hydrogenation in ethyl acetate at 0 °C.[49] The deliberate preparation of pure butyric acid requires harsher conditions, such as the use of a Raney nickel catalyst at 200 °C and at 150 atm of hydrogen.[50]

C. Ozonolysis

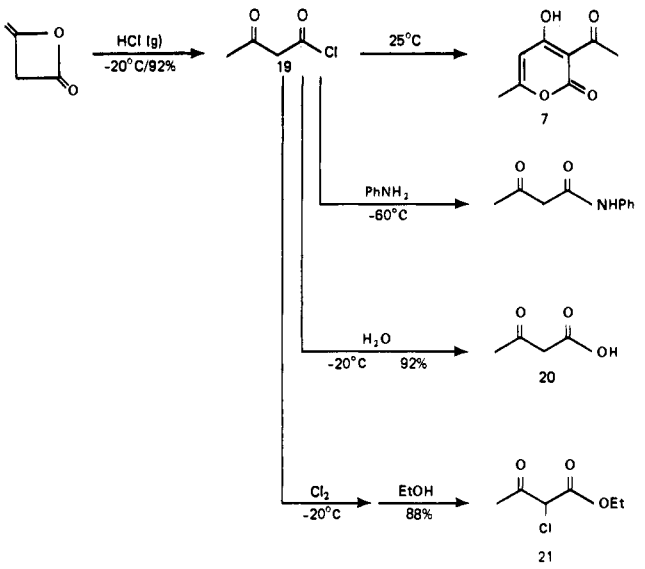
Low-temperature ozonolysis of diketene yields formaldehyde and malonic anhydride (18)[20,51,52] (Scheme VII). Malonic anhydride is thermally unstable and decomposes near 0 °C into carbon dioxide and ketene. This anhydride has been observed in solution by IR and NMR spectroscopy and has been converted into malonate derivatives in up to 76% yield by low-temperature reactions with simple nucleophiles such as aniline and ethanol.

D. Reactions with Hydrogen Halides

Diketene reacts with a slight excess of hydrogen chloride at low temperature to afford acetoacetyl chloride (19) in excellent yield.[17] Methylene chloride and carbon tetrachloride are good solvents for this reaction, and sulfuric and acetic acids have been used as reaction catalysts.[53]

Acetoacetyl chloride is used in situ at temperatures near −20 °C because it quickly dimerizes at 25 °C to form dehydroacetic acid (7) (Scheme VIII). Acetoacetic acid (20) can be prepared by hydrolysis of acetoacetyl chloride (19),[54] while chlorination of acetoacetyl chloride

SCHEME VIII



provides an intermediate for the preparation of 2-chloroacetoacetate esters (e.g., 21)[53] and 2-chloroacetoacetic acid.[54] Acetoacetyl chloride can be used as an alternative to diketene for acetoacetylation reactions.[17,55]

Diketene reacts with hydrogen fluoride at low temperature to provide acetoacetyl fluoride (22), which can be isolated (Scheme IX). Acetoacetyl fluoride has been used for the Friedel–Crafts acetoacetylation of a variety of benzene derivatives (see section III.G),[56] as well as for the preparation of 2-acetoacetylthiophene.[56c] The acidic reaction conditions used for the in situ generation of acetoacetyl fluoride usually result in the annulation of a methylcyclohexenone ring onto polycyclic aromatic compounds.

E. Halogenation

Elemental chlorine and diketene react to form 4-chloroacetoacetyl chloride (23), which, although more stable than acetoacetyl chloride, is still generally used in situ[16] (Scheme X). For example, a recent industrial preparation of ethyl 4-chloroacetoacetate (24) involved treating a dichloroethane solution of diketene with chlorine at 10 °C, followed by the addition of ethanol. The product was isolated in 90% yield and was free of the 2-chloro isomer.[57]

4-Chloroacetoacetyl chloride reacts further with chlorine to afford 2,4-dichloroacetoacetyl chloride (25), which is also readily derivatized to give dichloroacetoacetates.[58] At low temperatures, treatment of acetoacetyl chlorides with a stoichiometric amount of water is frequently used to form haloacetoacetic acids;[54] at elevated temperatures, decarboxylation of these acids provides acetone derivatives. This latter procedure is an excellent method for the preparation of chloroacetone (26),[59] dichloroacetone (27),[60] and other halogenated acetones.

The reactions of diketene with bromine are similar to those of diketene with chlorine, and mixed haloacetoacetates and haloacetones can thus be prepared. Bromoacetoacetate derivatives, however, are less stable than chloroacetoacetates and may rearrange to other bromoacetoacetate isomers.

Diketene reacts with *N*-bromosuccinimide to give

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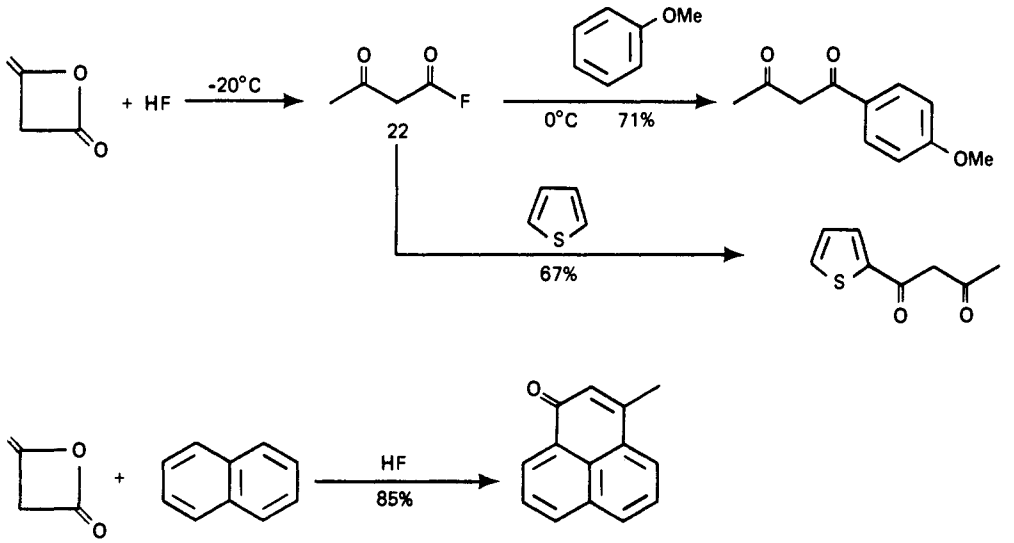
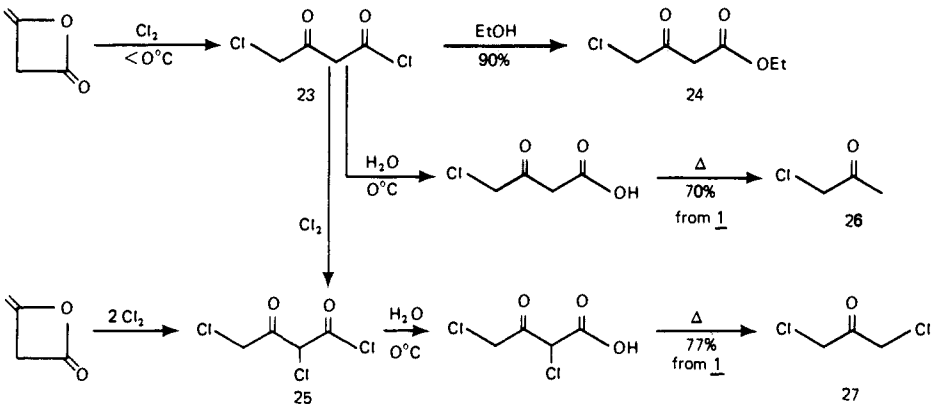


SCHEME X



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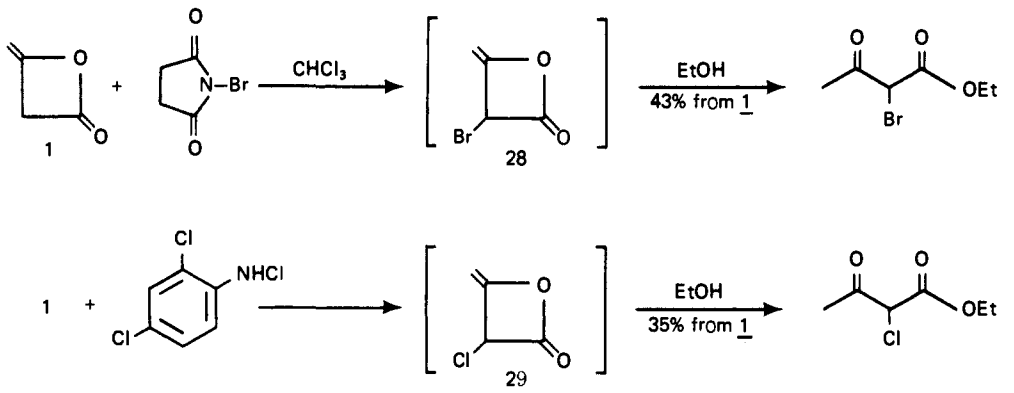


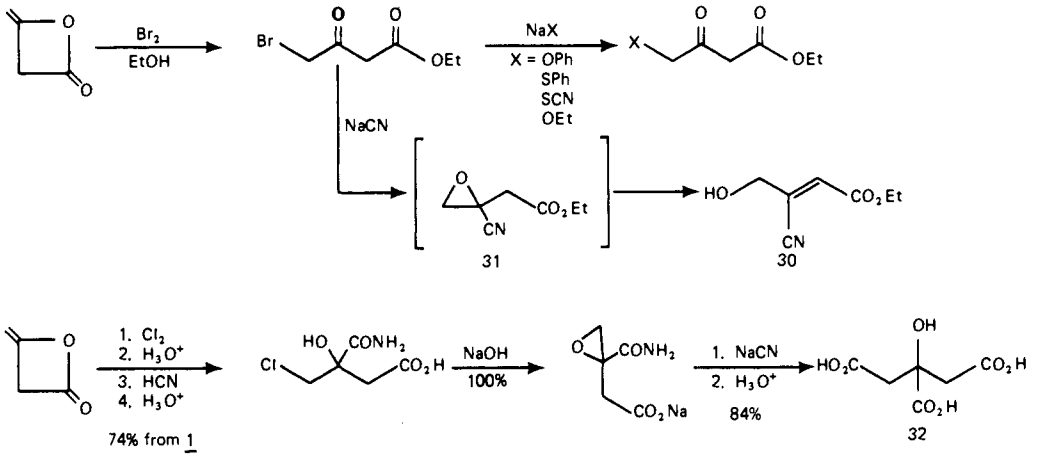
3-bromo-4-methylene-2-oxetanone (28), which can be trapped with ethanol at low temperature to provide ethyl 2-bromoacetoacetate in 43% yield[61] (Scheme XI). Likewise, diketene has been chlorinated in the 3-position with *N*,2,4-trichloroaniline to provide 3-chloro-4-methylene-2-oxetanone (29). These latter two reactions, in which the C-3 methylene group in the diketene ring is functionalized, appear to be the only known examples of this type of diketene reactivity. 2-Haloacetoacetate esters are more commonly prepared via halogenation of the corresponding acetoacetate ester.

Haloacetoacetyl halides, and the esters and amides derived therefrom, have found extensive use in organic synthesis. They have been modified by reduction, oxidation, displacement, heterocyclization, and a variety of other reactions. Unfortunately, no single source provides a comprehensive discussion of haloacetoacetic acid derivatives.

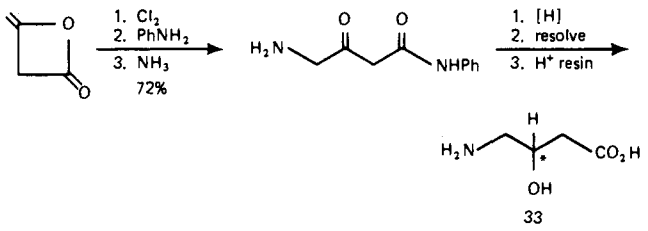
Most nucleophiles displace the halogen from 4-haloacetoacetates and acetoacetamides. The cyanide ion, however, attacks the carbonyl group and a rearranged product (30) is formed via an intermediate epoxide 31[62] (Scheme XII). A recent patent describes in detail an efficient synthesis of citric acid (32) from diketene via 4-chloroacetoacetic acid (isolated) and 3-carbamoyl-3,4-epoxybutyric acid.[63]

Triphenylphosphine[64] and sodium diethylphosphite[65] have both been used to displace bromine from 4-bromoacetoacetate esters and thus to prepare precursors to the phosphorus ylides used in Wittig and Hor-

SCHEME XII



SCHEME XIII



ner–Emmons olefination reactions.

The reduction of 4-functionalized acetoacetates derived from diketene provides a route to chiral 3-hydroxy-4-aminobutyric acids (**33**) and carnitine[66] (Scheme XIII).

Heterocyclization reactions which involve haloacetoacetate intermediates are discussed in a later section (V.E).

F. Nitrosation

The nitrosation of diketene illustrates the diverse reactivity which can be realized with different acetoacetic acid derivatives. Diketene reacts with sodium nitrite in ethanol to give α-oximino ester **34** and with isoamyl nitrite in HCl to afford the α-oximino ester **35**[67] (Scheme XIV). These reactions probably proceed via ethyl acetoacetate and acetoacetyl chloride, respectively. Ester **34** has been chemoselectively reduced to either the α-amino-β-keto ester or to racemic ethyl threonate (**36**).[68]

The preparation of β-halopyruvaldoximes **37** can be achieved by the nitrosation of 4-haloacetoacetyl halides in situ.[69] Nitrosation of ethyl 4-chloroacetoacetate, however, yields the α-oximino ester **38**, which cyclizes to **39** upon attempted distillation.[70] The nitrosation of ethyl 2-chloroacetoacetate resulted in deacetylation, thereby producing the hydroximinoyl chloride **40**.[70] A similar deacetylation has been observed during the reactions of 2-haloacetoacetates and 2-haloacetoacetamides with diazonium salts.[71]

G. Hydrolysis

In a pure form, diketene is only very slowly hydrolyzed when admixed with water. The initial product of the hydrolysis of diketene is acetoacetic acid, which subsequently decomposes to carbon dioxide and acetone.

A careful study of the hydrolysis of diketene in dioxane/water indicated that this reaction proceeds via nucleophilic ring opening of the acyl carbon–oxygen bond and that the addition of hydroxide ions promotes the rapid hydrolysis of diketene.[72] Pyridine accelerates the hydrolysis of diketene via nucleophilic activation, whereas the acetate anion accelerates hydrolysis by general base catalysis. The hydrolysis of diketene is pH insensitive under acidic conditions but sensitive to pH under basic conditions.[73]

Sodium tetrachloropalladate catalyzes the hydrolysis of diketene, and the palladium complex of acetoacetic acid can be isolated from the reaction mixture.[74] Crystalline acetoacetic acid has been prepared in 93% yield by acid-catalyzed hydrolysis of diketene, and it is stable for several months at 0 °C in the absence of light, air, and humidity.[75] The ^{1}H NMR spectrum of acetoacetic acid has been obtained in a variety of solvents.[54b]

Diketene can be carefully hydrolyzed in 10% aqueous sodium hydroxide to afford sodium acetoacetate (**41**), which can be conveniently used in situ as an acetone enolate equivalent for Knoevenagel reactions[76] and for the preparation of allylacetone[77] (Scheme XV).

The reaction of diketene and water, catalyzed by a tertiary amine, produces a mixture of 2,4,6-heptanetrione (**42**) and 2,6-dimethyl-4*H*-pyran-4-one (**43**).[78] The heptanetrione **42** is reported to control fungus on rice.[79]

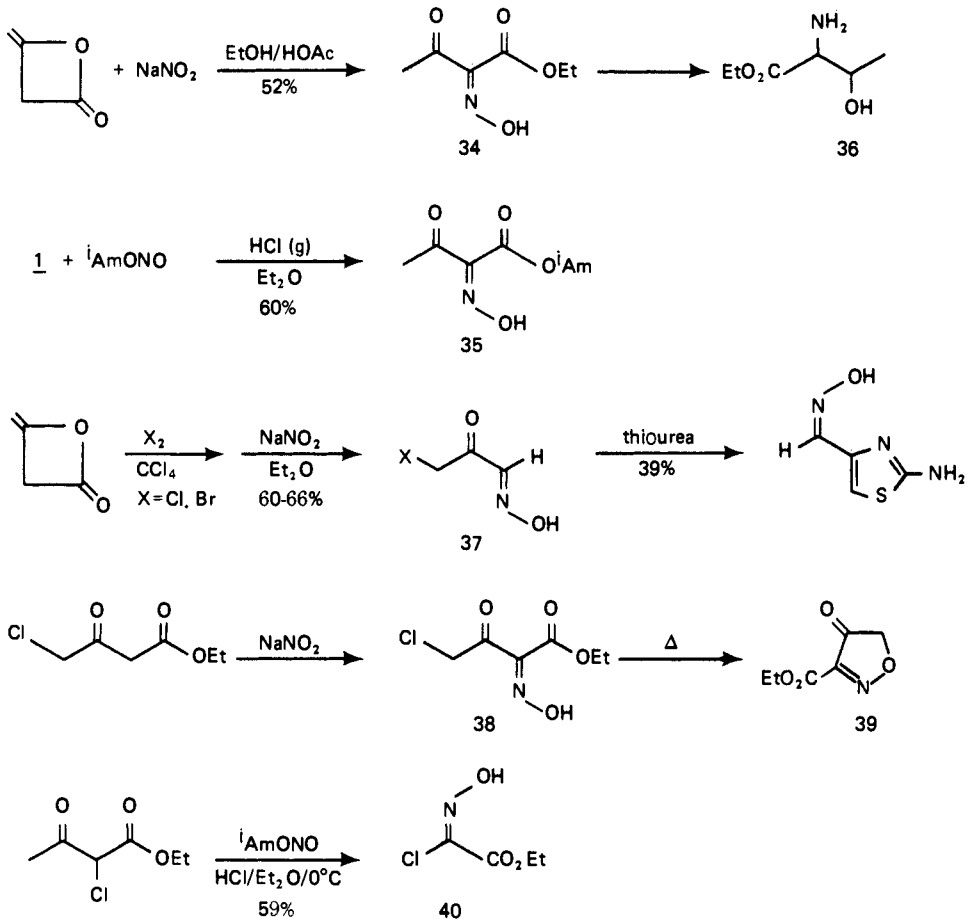
H. Ammonolysis

Treatment of diketene with ammonia can result in the formation of either acetoacetamide (**44**) or 3-aminocrotonamide (**45**) (Scheme XVI). Acetoacetamide is prepared by mixing stoichiometric quantities of diketene and ammonia in an inert solvent while the solution is cooled;[80] a 96% yield of acetoacetamide has thus been obtained.[81] The use of excess ammonia results in the direct formation of 3-aminocrotonamide (**45**) in yields of 90–94%. This latter compound has insecticidal properties and has also been found to stabilize vinyl polymers.[82]

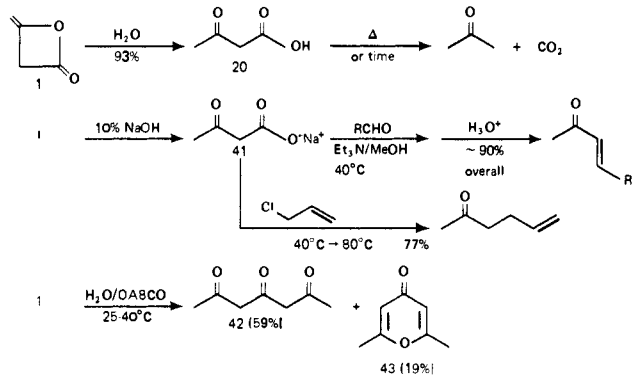
The closely related 3-aminocrotonate esters (**46**) can be prepared from acetoacetate esters by treatment with ammonium acetate in the presence of lead, zinc, lithium, or cadmium acetate.[83]

Heterocyclic synthesis with acetoacetamide and 3-

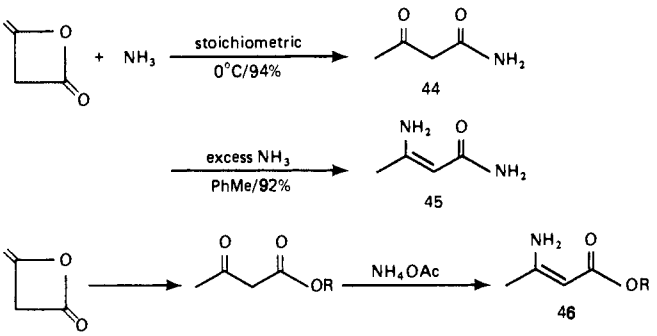
SCHEME XIV



SCHEME XV



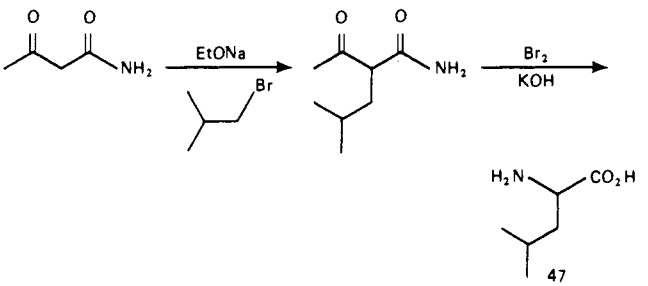
SCHEME XVI



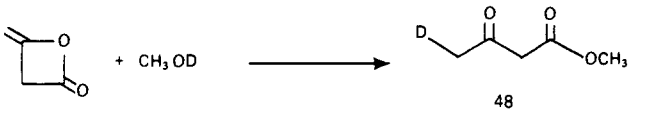
aminocrotonamide has been reviewed,[84] and the mechanism of the formation of 2,6-dimethyl-3*H*-4-pyrimidone by pyrolysis of 3-aminocrotonamide has recently been clarified.[85]

Acetoacetamide has been used in an unusual synthesis of leucine (47) (Scheme XVII). Thus, alkylation of the active methylene group of acetoacetamide with isobutyl bromide gave 2-isobutylacetoacetamide, which was converted into leucine via a one-pot Hofmann rearrangement and haloform reaction.[86]

SCHEME XVII



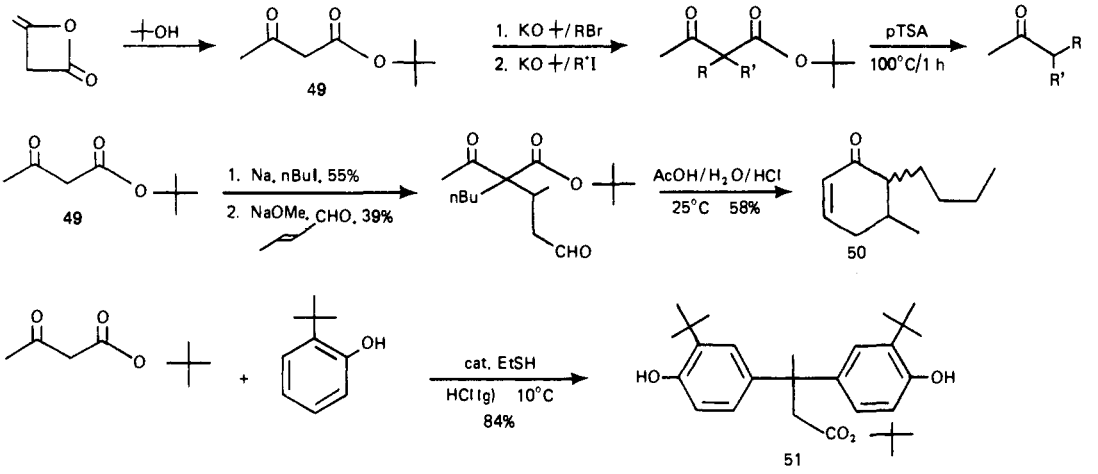
SCHEME XVIII



III. Acetoacetylation with Diketene

Most diketene is used for the preparation of acetoacetate esters and acetoacetamides, which are important synthetic intermediates used in the agrichemical, pharmaceutical, and dyestuffs industries. Because it is inexpensive and highly reactive, diketene is frequently the reagent of choice for acetoacetylations on both laboratory and industrial scales.

SCHEME XIX



This section of the review describes both acetoacetylation reactions and some applications of the acetoacetic acid derivatives thus formed. Reactions in which a substrate is acetoacetylated and then directly converted into a heterocycle are discussed in the heterocyclization sections (IV and V), where additional references to acetoacetylation reactions may be found.

A. Aliphatic Alcohols

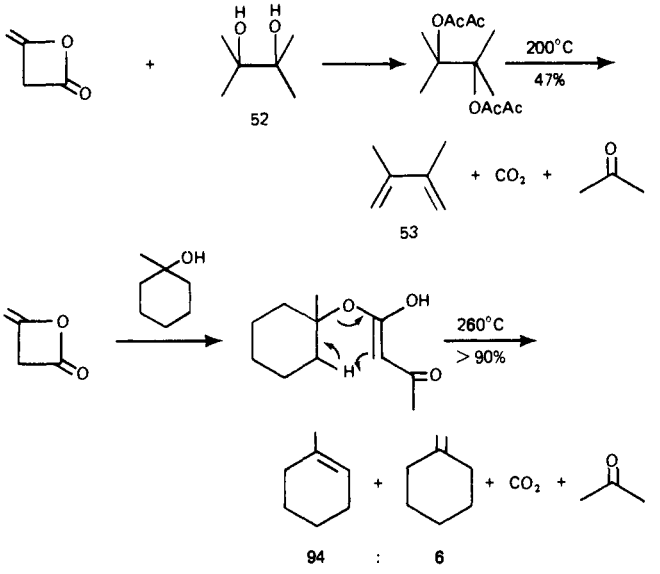
Like water, alcohols do not react rapidly with diketene at room temperature unless the reaction is catalyzed. Catalysts used for acetoacetylating alcohols have included pyridine,[87] 4-(dimethylamino)pyridine,[88] triethylamine[89] and other tertiary amines,[90] sulfuric acid,[91] tertiary phosphines,[92] sulfonic acids,[93] carboxylic acid salts,[94] hydroxides and alkoxides,[95] betaines,[92a] and sodium tetrachloropalladate.[96] Triethylamine, pyridine, and sodium acetate are the most widely used catalysts for laboratory acetoacetylation reactions.

Amine catalysts appear to ring-open diketene,[72,73] and an acetylketene–tertiary amine complex has supposedly been observed via infrared spectroscopy (at 2320 cm^{-1}).[97] This infrared absorption frequency, however, is closer to that of carbon dioxide (2349 cm^{-1}) than to a typical ketene absorption (~2150 cm^{-1}); this aspect of diketene chemistry bears further investigation.

Diketene acetoacetylates primary, secondary, and tertiary alcohols smoothly and is especially useful for reactions with hindered or otherwise unreactive alcohols. The relative reactivity of nucleophiles with diketene is in accord with empirical predictions of nucleophilicity; with the exception of amines and thiols, hydroxyl groups can be selectively acetoacetylated in the presence of most other functional groups. The reaction of diketene with deuteromethanol affords exclusively the 4-deutero compound **48** (Scheme XVIII), thereby demonstrating that the initially formed, unconjugated enolate can be trapped prior to isomerization.[98]

Laboratory-scale acetoacetylations of alcohols are often run in an inert solvent at, or slightly above, room temperature; a stoichiometric amount of diketene is used. On an industrial scale, acetoacetate esters are prepared in continuous reactors in which the alcohol, catalyst, and diketene are mixed together at elevated temperatures (50–150 °C) without an additional solvent.

SCHEME XX

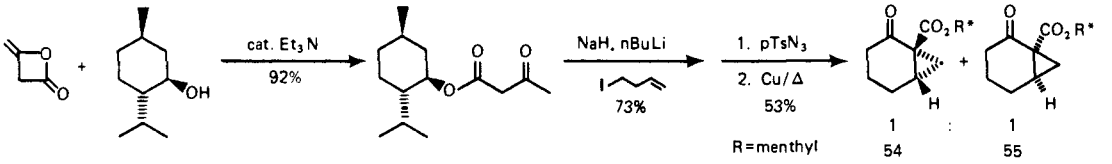


Numerous processes have been developed for the rapid and efficient preparation of methyl and ethyl acetoacetate.[90-95] These latter two esters are easier to handle than diketene, and are often transesterified with other alcohols in an alternate preparation of acetoacetate esters. An especially convenient preparation of acetoacetate esters utilizes the diketene/acetone adduct (see section VI.A).

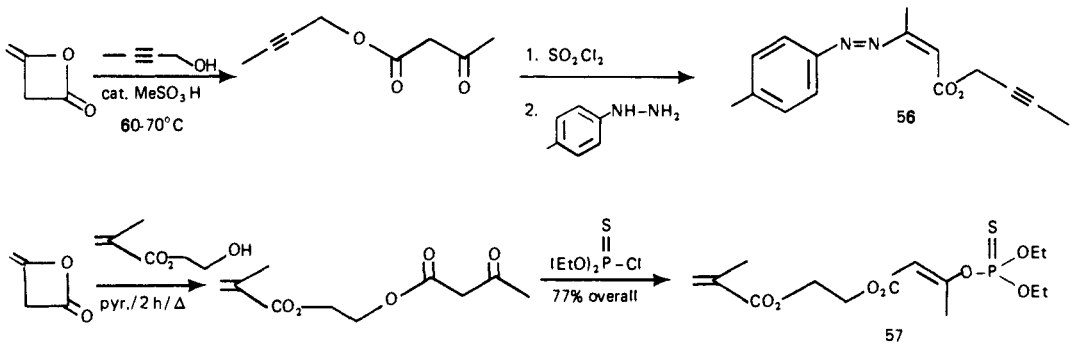
As with other diketene derivatives, most acetoacetate esters are used as synthetic intermediates. Acetoacetate esters are frequently converted into more highly functionalized β-keto esters via alkylation of the 2-methylene group or the 4-methyl substituent (via dianion chemistry).[99] The hindered *tert*-butyl acetoacetate (**49**), which is easily prepared from diketene and *tert*-butyl alcohol,[100] is an especially convenient acetone enolate equivalent because of its facile decarboxylation into gaseous products;[101] the synthesis of the cyclohexenone **50** is illustrative[102] (Scheme XIX). The preparation of 3,3-diarylbutanoates such as **51** demonstrates an alternate application of *tert*-butyl acetoacetate, in which all carbon atoms of the acetoacetate ester are retained.[103]

The hindered 2,3-dimethyl-2,3-butanediol (**52**) has been acetoacetylated with diketene and then pyrolyzed to give 2,3-dimethylbutadiene (**53**)[104] (Scheme XX).

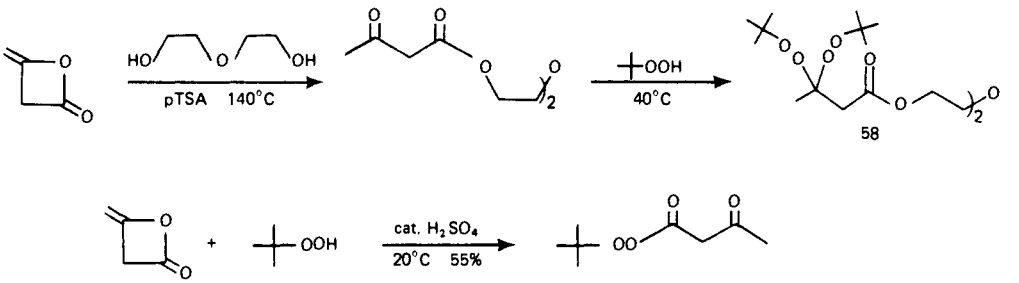
SCHEME XXI



SCHEME XXII



SCHEME XXIII

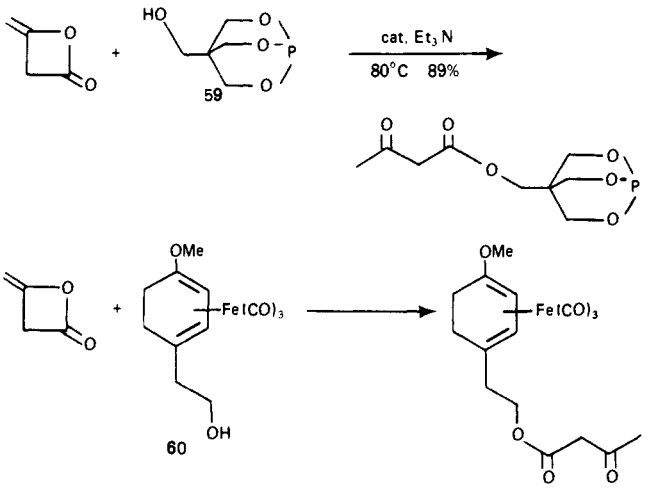


1-Methylcyclohexene has been similarly prepared from 1-methylcyclohexanol.[105] The dehydration of an alcohol by the pyrolysis of the corresponding acetoacetate derivative appears to be a general reaction of both tertiary and secondary alcohols; this dehydration occurs under neutral conditions at lower temperatures than are required for the pyrolysis of the corresponding acetate esters.[105b] In the formation of dimethylbutadiene **53**, the first elimination reaction would afford an allylic acetoacetate which should be susceptible to Carroll rearrangement (see section III.I). It would be interesting to know whether this side reaction accounted for the low conversion.

The dianion of optically pure menthyl acetoacetate was alkylated, and the resulting acetoacetate was diazotized and converted into the diastereomeric cyclohexanones **54** and **55** (Scheme XXI), which were separated by chromatography and then used as chiral synthons for the preparation of substituted cyclohexanones.[106] A series of chiral acetoacetate esters has been treated with hydride reagents, but the reductions proceeded with limited stereoselectivity.[107] Biochemical reductions of prochiral acetoacetic acid derivatives, however, are often both efficient and stereospecific, and are therefore preferred for the preparation of chiral 3-hydroxybutanoates.[108]

Acetoacetate esters of unsaturated alcohols are readily prepared with diketene,[87e] are requisite intermediates for the Carroll rearrangement (section III.I), and are also often used in the preparation of polymers (section III.H). Other acetoacetate esters which are derived from diketene and unsaturated alcohols have been converted into insecticides, such as **56**[93b] and **57**[87c]

SCHEME XXIV

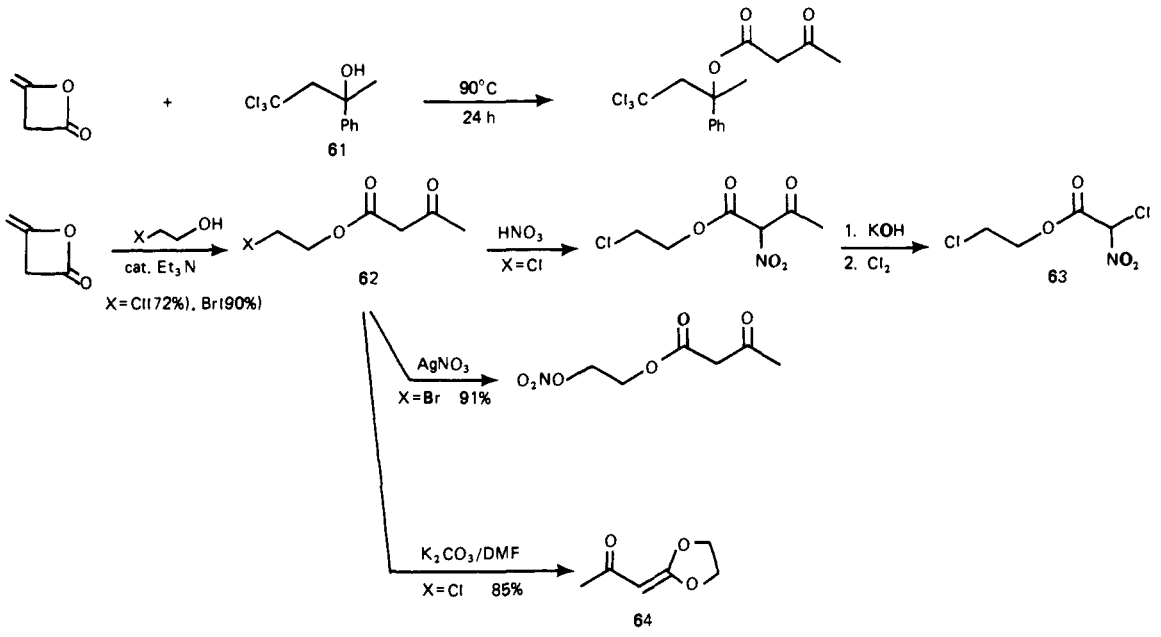


(Scheme XXII). A number of phosphate and thiophosphate enol esters of acetoacetic acid derivatives are used by the agrichemical industry.

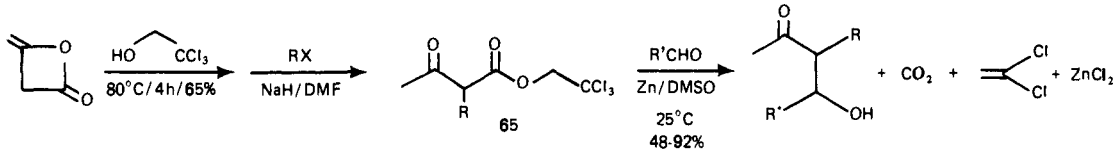
The bis acetoacetate of diethylene glycol can be ketalized with *tert*-butyl hydroperoxide to afford the radical initiator **58** ($t_{1/2}$ = 1 h at 135 °C)[93] (Scheme XXIII). *tert*-Butyl hydroperoxide itself is readily acetoacetylated with diketene.[109]

Hydroxyl groups can be acetoacetylated in the presence of various heteroatoms. (Dimethylamino)ethanol serves as its own catalyst[90a] during the preparation of 2-(dimethylamino)ethyl acetoacetate.[110] The phosphite ester **59** was treated with diketene to provide a nontoxic polypropylene stabilizer[90b] (Scheme XXIV). Hydroxyl groups adjacent to phosphonate esters are readily ace-

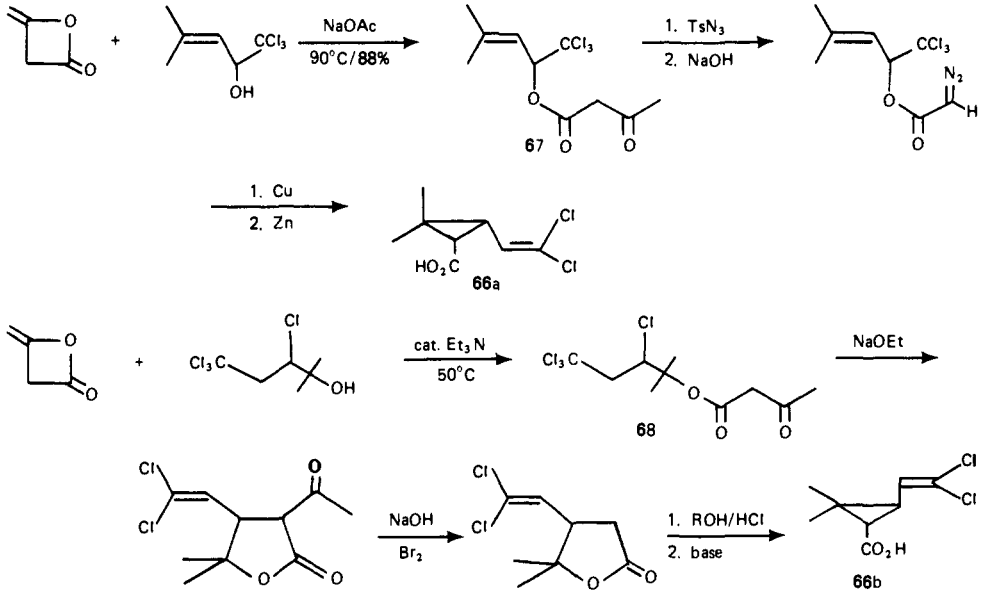
SCHEME XXV



SCHEME XXVI



SCHEME XXVII



toacetylated at 50 °C with diketene, whereas they only react poorly with ethyl acetoacetate, even under forcing conditions.[111] Organoiron compound **60** has been acetoacetylated by diketene without event.[112]

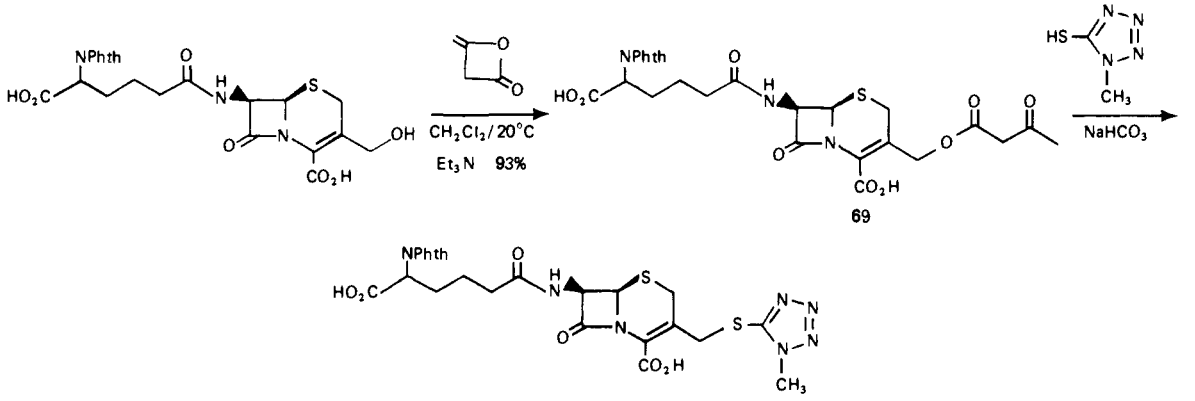
Diketene is sufficiently reactive to acetoacetylate alcohols that contain electron-withdrawing substituents, including trifluoroethanol[113] and the halogenated, tertiary benzylic alcohol **61**.[114] Diketene, via haloethyl acetoacetates **62**, has been used to prepare halonitroacetate ester **63**,[91a] nitroalkyl acetoacetates,[115] and acetylketene acetal **64**[116] (Scheme XXV).

The zinc-catalyzed cleavage and anion generation from trichloroethyl acetoacetate esters **65** provides a method for preparing β-hydroxy ketones[117] (Scheme XXVI).

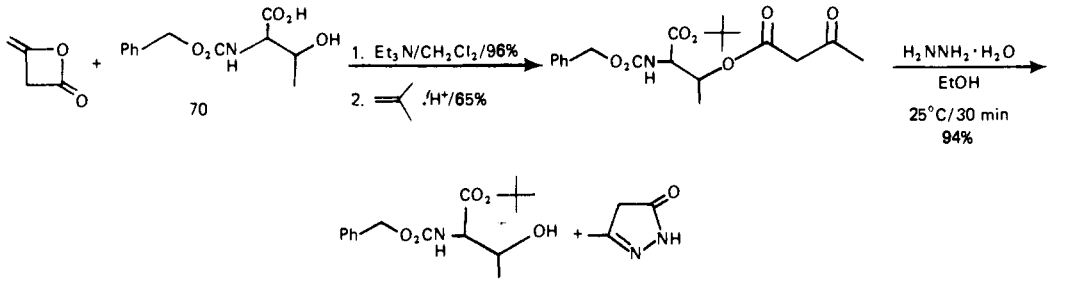
Acetoacetate esters of several nonnucleophilic alcohols have been prepared from diketene and used for the preparation of pyrethroid insecticide precursors, such as **66**. One such approach to the cis isomer **66a** involved diazotization and deacetylation of the active methylene group of acetoacetate **67**,[118] while the trans isomer **66b** was prepared by an intramolecular S_N2' displacement reaction on the intermediate resulting from dehydrochlorination of acetoacetate ester **68**[119] (Scheme XXVII).

Cephalosporins can be readily acetoacetylated on the

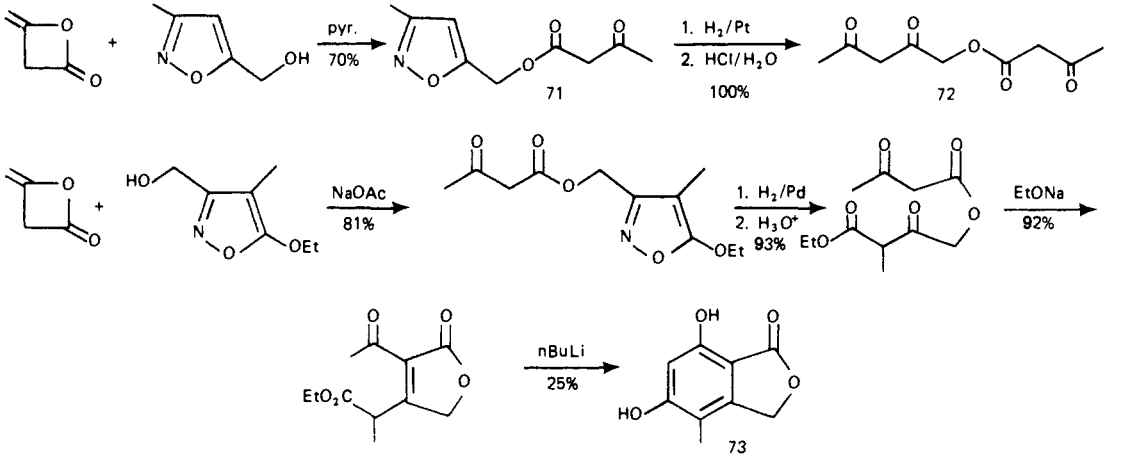
SCHEME XXVIII



SCHEME XXIX



SCHEME XXX

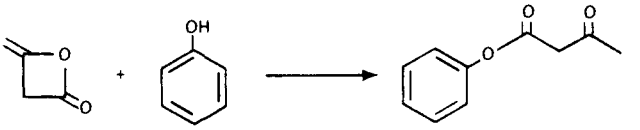


3-hydroxymethyl side chain, and the resultant allylic acetoacetates (e.g., **69**) are readily displaced by nucleophiles (Scheme XXVIII). This acetoacetylation/displacement sequence is routinely used to attach the side chains present in many commercial β-lactam antibiotics; yields are excellent, and carboxylic acids need not be protected.[120] In fact, the acetoacetyl group will protect the C-3 hydroxymethyl group during removal or alteration of the C-7 acyl side chain.[121]

The use of diketene to protect hydroxyl groups during peptide synthesis has been demonstrated with *N*-[(benzyloxy)carbonyl]threonine (**70**); the acetoacetate group was removed with hydrazine[122] (Scheme XXIX). Diketene has also been used as an N-protecting group, as discussed in section III.C. Diketene could become valuable as an economical protecting reagent if additional methodology for its removal were to be developed.

Some compounds of medicinal interest have been acetoacetylated to increase their lipophilicity. The β-dicarbonyl compounds which result from aceto-

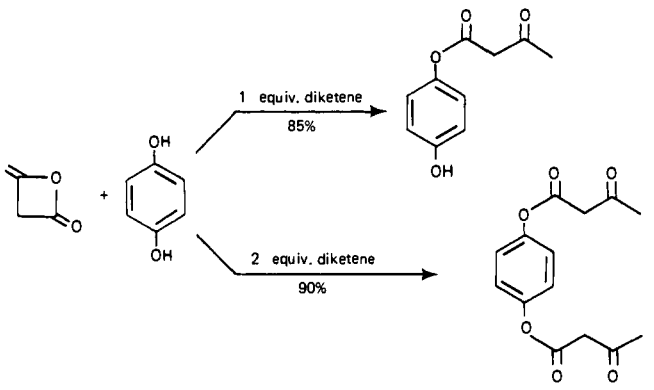
SCHEME XXXI



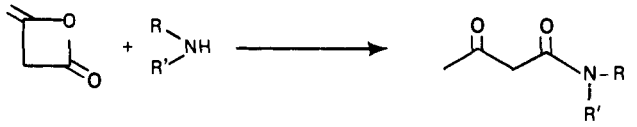
acetylation with diketene are known to enhance drug absorption in the small intestine.[123] The coadministration of either glycerol-1,3-diacetoacetate or 1,2-isopropylideneglycerol-3-acetoacetate with insulin enhances rectal absorption of the insulin.[123b] Glycerol monoacetoacetate has been used as an alternative to glucose for parenteral nutrition.[124] In addition, several acetoacetylated steroids exhibit fertility controlling (progestational) activity.[125] Cassaine, a cardiotonic agent, has also been modified by acetoacetylation.[126]

The transformation of isoxazoles into β-dicarbonyl compounds can be used to convert acetoacetylated isoxazoles (e.g. **71**) into poly-β-dicarbonyl compounds such as **72**[127] (Scheme XXX). Several phthalide derivatives,[128] including a precursor (**73**) to mycophenolic

SCHEME XXXII



SCHEME XXXIII



acid,[129] have been prepared from such acetoacetylated isoxazoles.

B. Phenols

Both acidic[130,91a] and basic[131,87d,90c] catalysts have been employed in the acetoacetylation of phenols with diketene, although triethylamine is most frequently used. The preparation of aryl acetoacetates proceeds rapidly when electron-rich phenols are used (Scheme XXXI). However, under acidic conditions, the resulting acetoacetates may undergo subsequent ring-closure to form coumarins (see section IV.H).

Neither pyridine nor sulfuric acid will catalyze the acetoacetylation of the more acidic phenols by diketene,[131] but even *p*-nitrophenyl acetoacetate has been prepared by the triethylamine-catalyzed, 25 °C reaction of *p*-nitrophenol and diketene.[132]

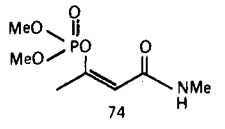
With hydroquinone, it is possible to achieve selective mono- or diacetoacetylation by controlling the stoichiometry of the reaction[131a] (Scheme XXXII).

The acetoacetate esters of 1- and 2-naphthols have been coupled with diazonium salts to give dyes which are used in the textile industry.[133,87e]

C. Aliphatic Amines

Primary and secondary aliphatic amines are rapidly acetoacetylated by diketene (Scheme XXXIII). No catalyst is required.

Recent patents describe continuous processes for preparing aliphatic acetoacetamides. Oftentimes the aliphatic amine and diketene are mixed at a temperature slightly above the melting point of the amine; yields of 96–100% are reported.[134] Several acetoacetamides which are produced from small aliphatic amines are commodity chemicals which are heavily used in the preparation of insecticides such as monocrotophos (**74**, Azodrin), dicrotophos, and phosphamidon.



74

The pesticide oxamyl (**75**) is prepared from *N,N*-dimethylacetoacetamide, as shown in Scheme XXXIV.[135] Tranquilizing compounds, such as **76**, have been based on 3-hydroxybutyramide derivatives which are readily accessible from diketene and 2-ethylhexylamine.[136]

An extensive series of 2,3-dioximidobutyramides (**77**) has been prepared from acetoacetamides[137] (Scheme XXXV), and these functionalized butyramides have been used to form orange-colored nickel chelates that are useful in inks and dyes.[138] Other dyes, such as **78**, have been prepared by coupling diazonium salts with acetoacetamides.[139]

Acetoacetamides react with benzofurazan oxides in a modification of the Beirut reaction[140] to afford bactericidal quinoxaline *N,N*-dioxides[141] (Scheme XXXVI). These quinoxaline dioxides, of which olaquindox (**79**) is an example, are used as feed additives to promote animal growth. Several procedures for preparing the *N*-(2-hydroxyethyl)acetoacetamide, which is used in olaquindox, have been published,[142] and analogues of **79** continue to be reported.

Treatment of acetoacetamides or acetoacetanilides with sodium hypoiodite results in deacetylation to afford diiodoacetates. This latter technique is quite general, and has been used to prepare the iodo analogue (**80**) of chloroamphenicol[143] (Scheme XXXVII).

Diketene was converted into an ethylene bridge during the preparation of compounds (e.g., **83**) which are active against Parkinsonism. Thus, amino alcohol **81** was acetoacetylated and then converted into diazoacetate **82**, which was cyclized and reduced[144] (Scheme XXXVIII).

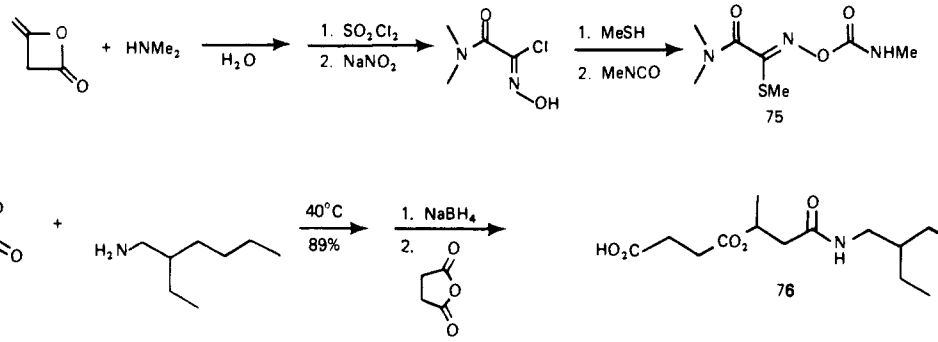
Acetoacetamides have been used in several preparations of β-lactams. Workers at Beecham Laboratories have acetoacetylated perhydrooxazine **84** with diketene and then diazotized and cyclized the resulting acetoacetamide (**85**) to provide a versatile intermediate for the preparation of thienamycin (**86**) derivatives[145] (Scheme XXXIX); the use of a chiral oxazine has recently been used to make this synthesis stereospecific.[146] The pyrrolidinone **87**, which is produced from the acid-catalyzed reaction of diketene and the protected aminomalonate **88**, has also been transformed into thienamycin.[147] Diazoacetamide **89** was used to prepare the biologically inactive tricyclic β-lactam **90**.[148]

The amino group of 7-aminocephalosporanic acid (7-ACA) is rapidly acetoacetylated at 0 °C to provide a product which exhibits modest antibiotic activity.[149] 6-Acetoacetamidopenicillanic acid can be coupled with nitrile oxides to afford isoxazole side chains, such as the one in dicloxacillin (**91**)[150] (Scheme XL). Other β-lactams have also been N-acetoacetylated with diketene.[151]

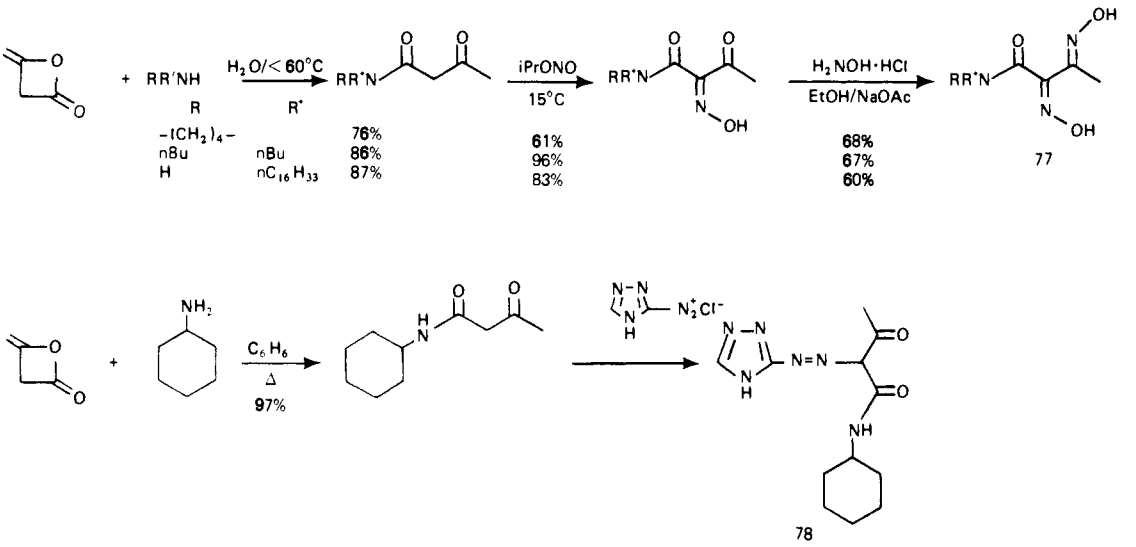
Diketene has been used to introduce amino acids onto peptides. Phenylalanine was acetoacetylated and treated with hydrazoic acid to effect a Schmidt reaction which provided *N*-(acetylglycyl)phenylalanine (**92**)[152] (Scheme XLI). This latter reaction sequence has been used with 2-alkylated acetoacetates to prepare a variety of dipeptides.[153] Acetoacetylation of ethyl glycinate, followed by diazotization and reduction, results in the attachment of a DL-allothreonine unit onto a peptide.[154]

Diketene was first suggested as an N-protecting group for peptide synthesis in 1965, when an N-acetoacetylated dipeptide was deacetoacetylated with phenylhydrazine.[155] The efficient use of diketene as an

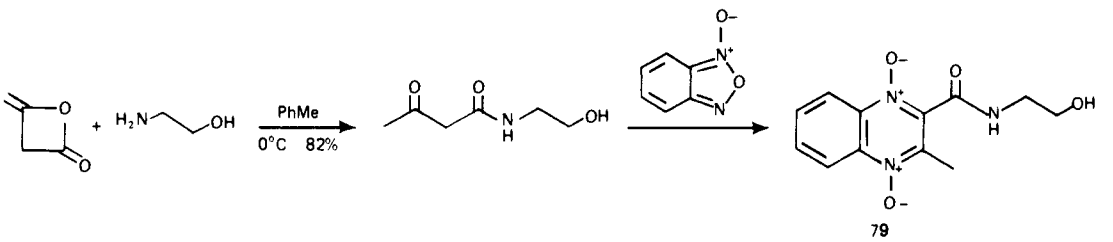
SCHEME XXXIV



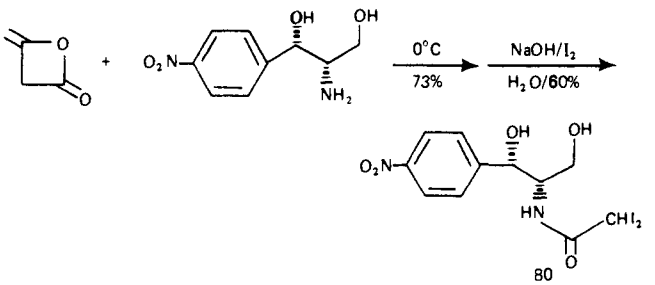
SCHEME XXXV



SCHEME XXXVI



SCHEME XXXVII



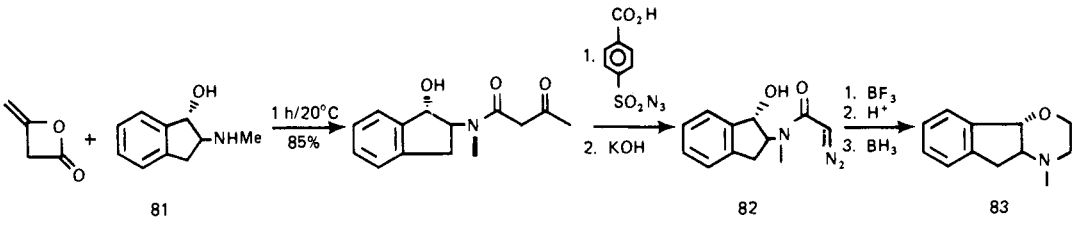
N-protecting group was demonstrated in a recent synthesis of aspartame (**93**). Thus, aspartic acid was acetoacetylated with diketene in aqueous base and then converted into acetoacetamidoaspartic anhydride, which was coupled with phenylalanine methyl ester. The resulting product was smoothly deacetoacetylated with hydroxylamine to provide the artificial sweetener **93**.[156]

Large molecules, such as polypeptides, can often be efficiently and selectively acetoacetylated with diketene; the resulting derivatives often show markedly altered activity. For example, insulin can be specifically acetoacetylated on the amino terminus of the β-chain. This reaction provides a derivative with 75–90% of the blood sugar lowering activity of insulin but with only 10% of its immunoreactivity.[157]

Studies on the acetoacetylation of flagellin with diketene showed amino groups to be functionalized in preference to hydroxyl groups and the resulting derivatives to be unaffected by antiflaggellin antibodies.[158] However, thiol residues, such as those in acetylcoenzyme A, are rapidly acetoacetylated with diketene; dethioacetoacetylation was accomplished with sheep liver deacylase.[159]

Diketene has been used as a reversible blocking group for free amino groups on enzymes.[160] Transfer ribonucleic acid (t-RNA) is reversibly inactivated by a 15-min treatment with diketene; hydroxylamine was used for deacetoacetylation.[161] Guinea pig ileum histamine and acetylcholine receptors are inhibited when treated with diketene,[162] as is deoxyribonucleic acid (DNA)

SCHEME XXXVIII



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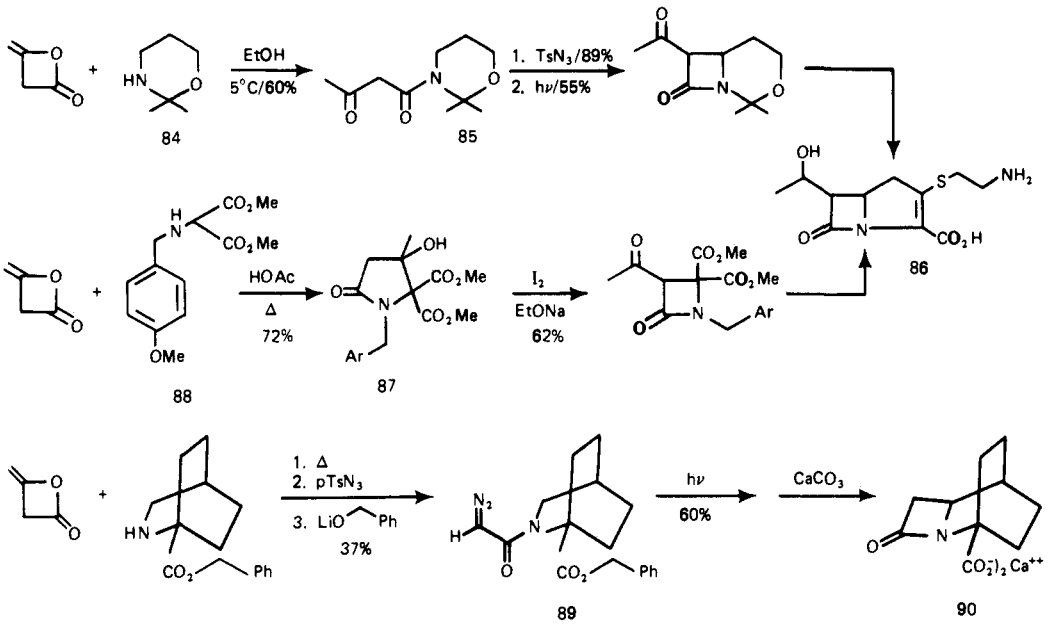
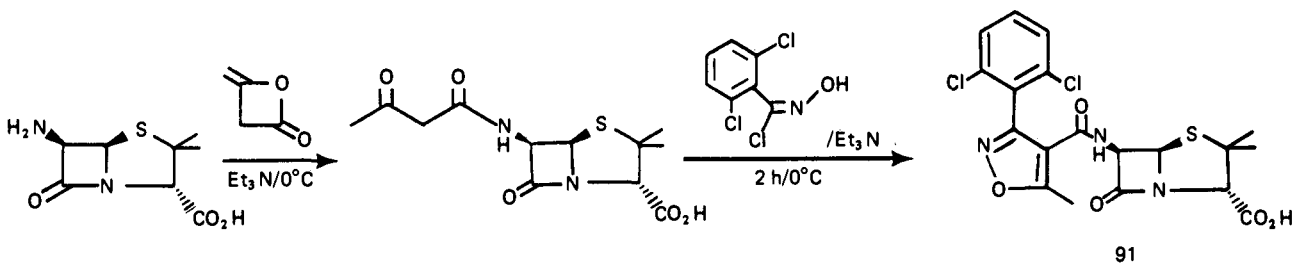


SCHEME XL



photolyase.[163] Also, acetoacetylation of α-globulin provides a product which is suitable for intravenous administration.[164]

Long chain aliphatic amines and polyamines have been acetoacetylated with diketene to afford acetoacetamides. These acetoacetamides are useful as cellulose ester plasticizers, lubricating oils and greases, and for improving metal adhesion.[165]

Aliphatic acetoacetamides that are used by the polymers industry are discussed in section III.H.

D. Aromatic Amines

Aromatic amines react with diketene to yield acetoacetarylides (**94**)[9a] (Scheme XLII); the rates of these acetoacetylation reactions increase with increasing basicity of the amines.[166]

While a catalyst is often not necessary, acetoacetarylide formation may be accelerated by adding a tertiary amine,[167] a mercury salt,[168] or an acid (HCl or HOAc)[169] catalyst. Water and water-soluble alcohols are the commonly used solvents, and yields in excess of 90% are generally realized.[170]

Several acetoacetarylides, such as those derived from aniline or toluidine, are commodity chemicals heavily used for the preparation of yellow, orange, and red dyes.[171] For example, acetoacetanilide can be coupled with the diazonium salt of 3,3'-dichlorobenzidine (**95**) to afford a yellow pigment (**96**) known as pigment yellow 12 (Scheme XLIII), which accounts for over half of the total U.S. production of organic yellow pigments. Likewise, approximately one-quarter of the total U.S. production of orange pigments is that of pigment orange 16, which is derived from 3,3'-dimethoxybenzidine and acetoacetanilide.

Some other dye couplers include 4-chloro-2,5-dimethoxyacetoacetanilide (HR coupler)[172] and 4-acetoacetamidobenzenesulfonic acid.[173] The alkylation of several dyes which were prepared from acetoacetanilides and aryl diazonium salts has been studied.[174]

Diketene has been incorporated into many other azo dyes,[175] some of which have been metalized;[176] the or-

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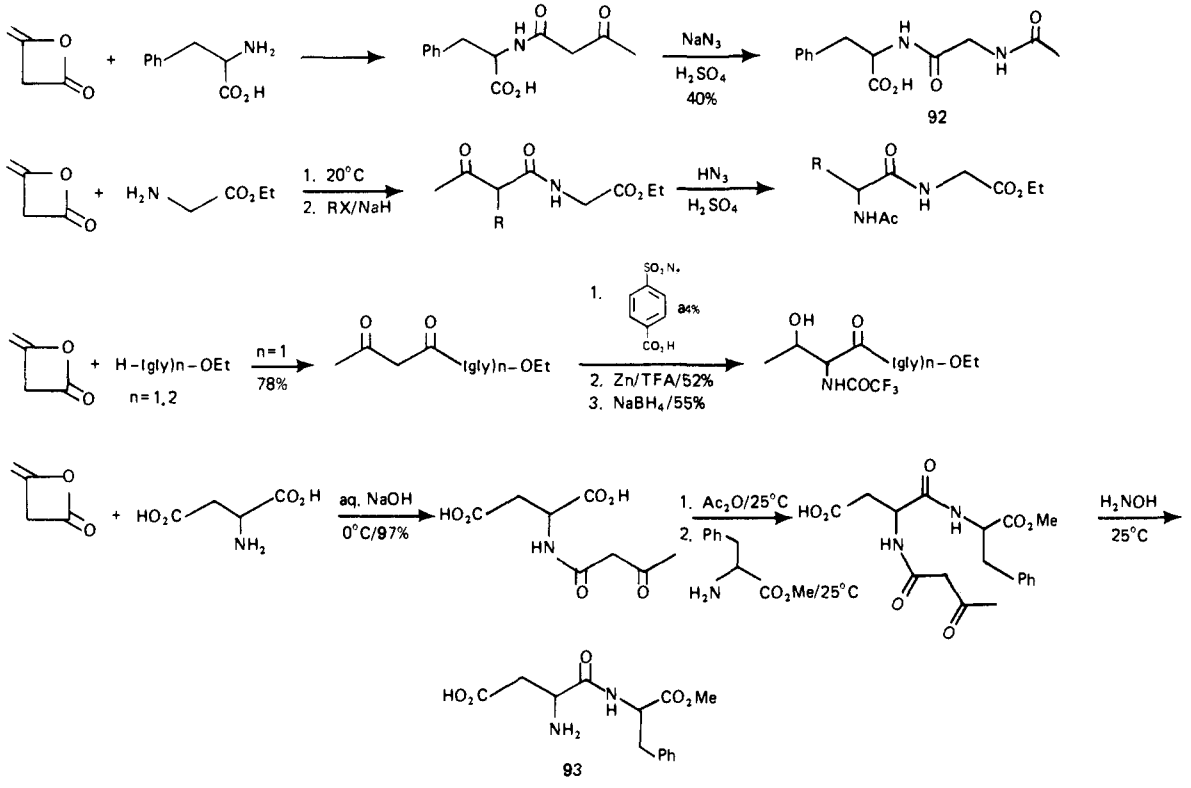
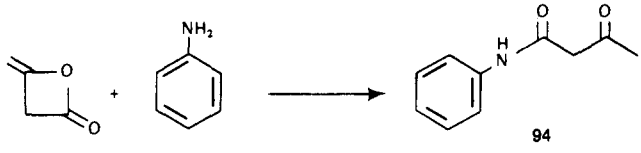


SCHEME XLII



ange-colored cobalt complex **97** is illustrative.[177] A nickel chelate (**98**), based on acetoacetanilide **99**, was prepared by nitrosation and oximation of the arylide prior to metalation[138] (Scheme XLIV).

A number of acetoacetarylides have been prepared from anilines of pharmaceutical and agricultural interest in the search for enhanced biological activity.[178] Several acetoacetarylides have been further converted into herbicidal 3-methoxycrotonanilides (**100**)[179] (Scheme XLV).

The acid-catalyzed cyclization of acetoacetarylide cyanohydrins has been used to make pyrrolidine-2,5-diones, such as **101**[180] (Scheme XLVI).

E. Heterocyclic Amino Groups

There are relatively few examples of acetoacetylation of heterocyclic amino groups in which the ultimate goal was not subsequent ring closure to form a new heterocycle (see sections IV and V). These acetoacetylations are usually straightforward in those instances in which there are no pathways for intramolecular cyclization.

Several heterocyclic acetoacetamides, such as 5-acetoacetamidobenzimidazolone (**102**) have been used in the preparation of dyes.[181] Diketene has also been used to convert a 3-morpholino-1,2,3-oxadiazolium salt (**103**) into an ylide (**104**) which has antihypotensive properties[182] (Scheme XLVII). The heterocyclic acetoacetamide **105** has proven useful as a plant growth regulator.[183] Benzotriazine 1,4-dioxide **106** can be acetoacetylated to afford bactericide **107**, which is claimed to be useful as a growth promoter in animals (see compound **79**).[184]

In acetone, the amino group of heterocycle **108** is readily acylated with diketene to afford the corresponding acetoacetamide (Scheme XLVIII). If this latter reaction is run in water, however, the isolated product is the acetoacetate salt of the protonated heterocycle.[185]

F. Other Functional Groups

Diketene acetoacetylates *N*-arylhydroxylamines (e.g., **109**) to afford *N*-arylacetoacetohydroxamic acids such as **110**[186] (Scheme XLIX). When this acetoacetylation reaction is run with excess diketene (phenylhydroxylamine, chloroform, reflux), a small amount (4%) of *o*-acetonylacetanilide is formed in addition to **110**, presumably via the N,O-diacetoacetylated compound.[187] This rearrangement reaction has been developed into a viable synthetic procedure. Thus, *N*-phenylacetohydroxamic acid (**112**) can be acetoacetylated with diketene, and the resulting compound (**113**) will rearrange to the ortho-substituted anilide upon heating.[188] The *N*-hydroxyacetoacetanilides **110** are bidentate ligands which chelate strongly with many metal ions.[189]

Most reactions between diketene and hydroxylamines are used for the preparation of isoxazole derivatives, as is discussed in section V.B. Oximes are exothermically O-acetoacetylated by diketene in the presence of an amine catalyst.[190]

Amides have been acetoacetylated with diketene in refluxing benzene or at room temperature in the presence of trimethylsilyl iodide[191] (Scheme L). Early attempts to acetoacetylate *N*-trimethylsilyl amides under

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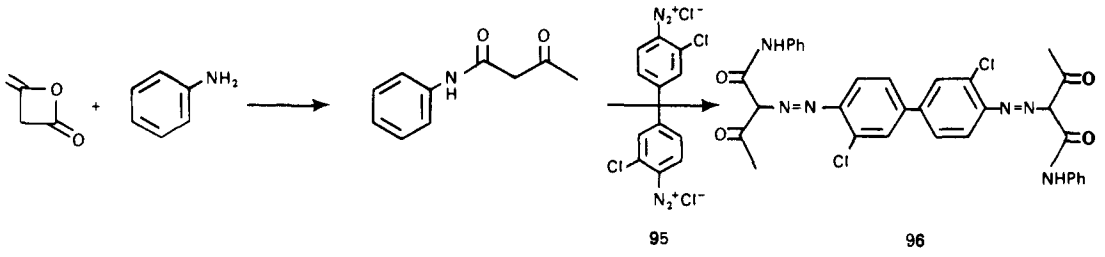
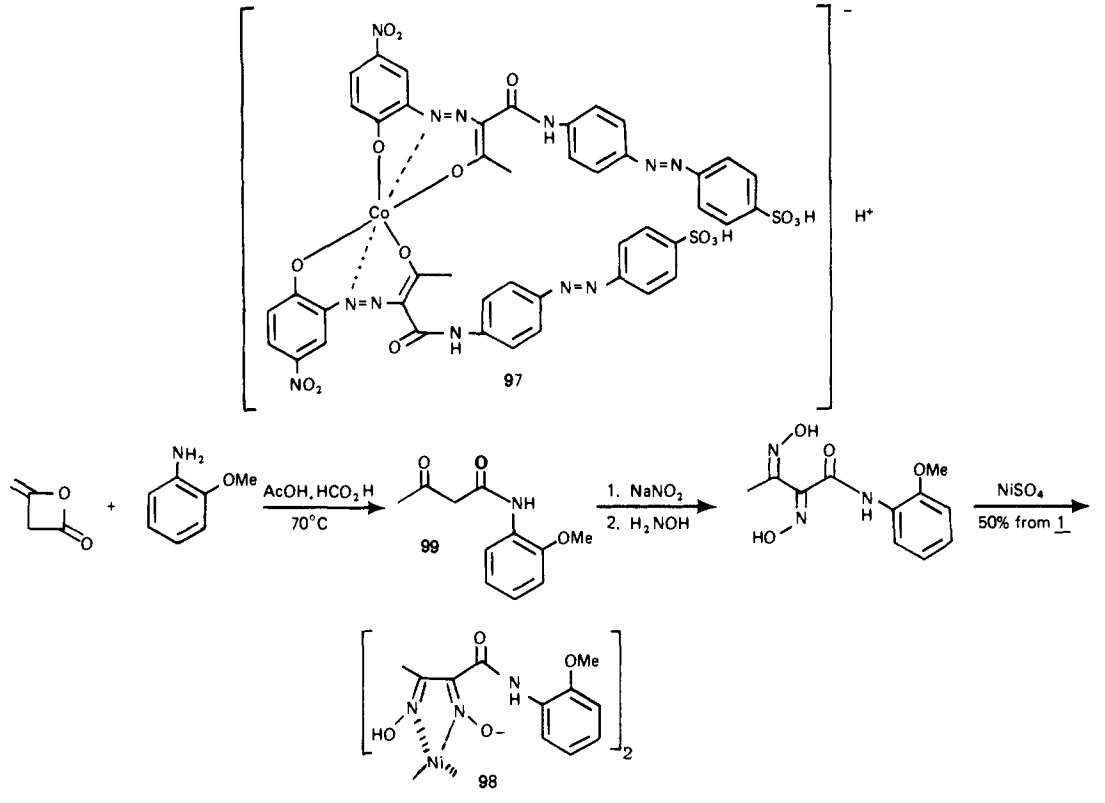


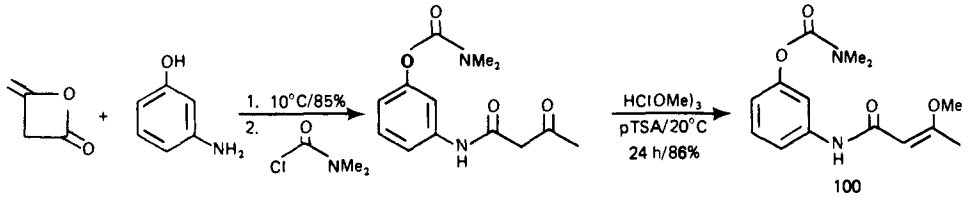
95 96

SCHEME XLIV



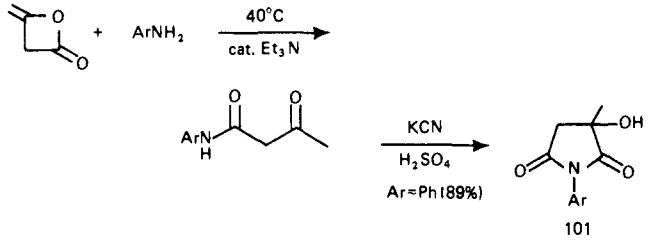
97 99 98

SCHEME XLV



100

SCHEME XLVI



101

basic conditions were somewhat less successful and were complicated by further reaction of the products with additional diketene.[192] Quaternary ammonium halides also catalyze the acylation of amides by diketene.[193]

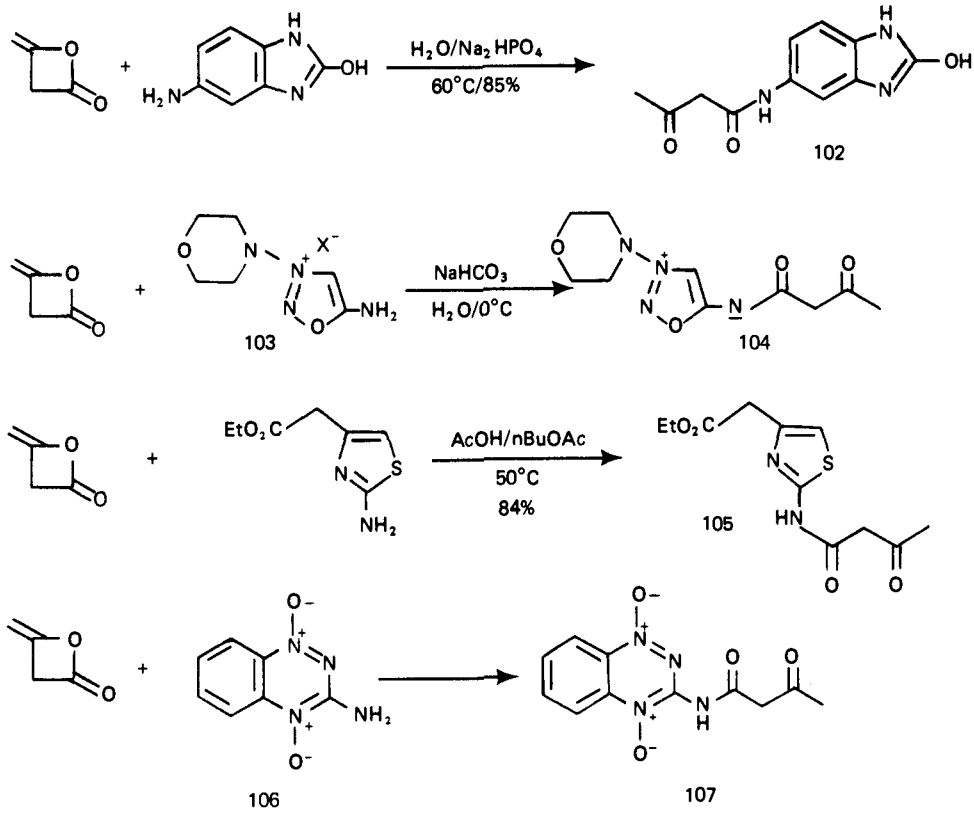
Mercury salts catalyze the reaction of diketene with various weak nucleophiles and have been used in the preparation of an insecticide (114) from an amide and diketene[194] (Scheme LI).

Ureas can be acetoacetylated with diketene in the presence of mercury salts (Scheme LII); further cyclization to uracils often occurs under the stringent reaction conditions which are required when a catalyst is not present.[195]

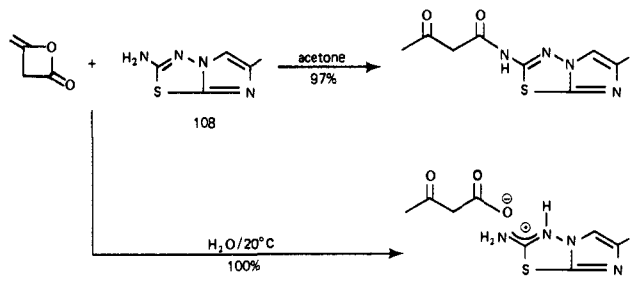
In the presence of a strong base, sulfonamides can be acetoacetylated to provide *N*-acetoacetylsulfonimides, which are useful as dye intermediates[196] (Scheme LIII). In this latter reaction, it is necessary to add the base and the diketene to the reaction vessel separately but simultaneously. Sulfamoyl fluoride (115) is easily acetoacetylated with diketene under mild conditions to furnish an intermediate which is used in the preparation of the artificial sweetener acesulfame K (116).[197]

Thiols are acetoacetylated with diketene under basic

SCHEME XLVII



SCHEME XLVIII



conditions,[198-200] provide 3-substituted crotonic acids (117) under acidic conditions,[198] and can also undergo facile radical additions to the double bond of diketene (see section VI.B.1) (Scheme LIV). The synthesis and hydrolysis of thiol acetoacetates has been examined in detail;[199] the spectral properties (IR, NMR) of these compounds have been analyzed.[200] A series of thiol acetoacetates has been converted into thio enol ethers.[200] Dodecyl thioglycolate *S*-acetoacetate is claimed to be a heat stabilizer for polyvinyl chloride compounds.[201]

Diketene reacts with sodium *tert*-butylthiolate to afford *tert*-butyl acetothioacetate (118), which can be alkylated specifically in the 2- or 4-position or can be transesterified (Scheme LV). Compound 118 has been used in the synthesis of two mold metabolites (see section IV.L).[202]

Thiophosphonate esters can be slowly acetoacetylated under mild conditions to afford the mixed anhydrides 119 and 120 (Scheme LVI). Compound 119 rearranges to an isopropenyl thiophosphonate ester upon heating; this reaction more likely proceeds via an intramolecular attack by sulfur on the ketone of 119 than via a thermal reversion to diketene as suggested in the reference.[203]

The formation of dehydroacetic acid (DHA, 7) from 120 closely resembles the self-condensation of acetoacetyl chloride to form DHA.

There is one report of the acetoacetylation of selenophenol with diketene, in the presence of *p*-toluenesulfonic acid; this product might actually be 3-(phenylselenyl)crotonic acid (see compound 117).[204]

Anhydrides can be conveniently prepared by decomposition of acetoacetic mixed anhydrides, which are made from a carboxylic acid and diketene[205] (Scheme LVII). Thus, a carboxylic acid can be stirred with diketene at room temperature and the desired anhydride can be isolated upon distillation. This latter reaction has also been used for the preparation of pyrophosphate tetraesters from phosphoric acid diesters.[206]

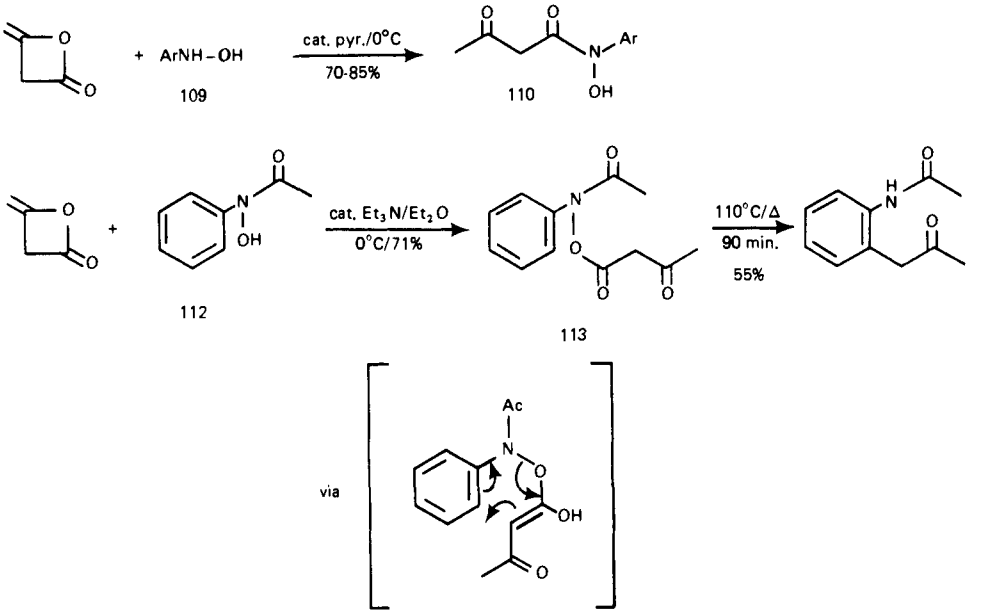
G. Acetoacetylation at Carbon

Under neutral conditions, diketene and indole combine to afford 1-acetoacetylindole (121),[207-209] but 3-acetoacetylindole (122) is produced when the reaction is run in hot acetic acid[208] (Scheme LVIII). Some 3-acetoacetylindoles have been used as intermediates for the preparation of other 3-acylindoles,[208] and several 2-alkyl-3-acetoacetylindoles are claimed to be sedatives and analgesics.[210]

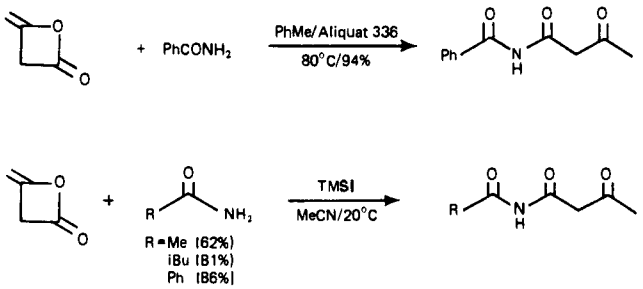
2-Acetoacetylpyrrole (123) is readily prepared by the −5 °C, pyridine-catalyzed reaction of pyrrole and diketene (Scheme LIX); earlier findings[209] that this reaction proceeded at 50 °C in the absence of a catalyst probably involved impure pyrrole.[211] The acylation of some substituted pyrroles with diketene has also been investigated,[209] and acetoacetylpyrrole has been used in the synthesis of some complex benzo[1,2-*b*:4,3-*b*']-dipyrroles.[211]

Diketene has been used for Friedel–Crafts aceto-

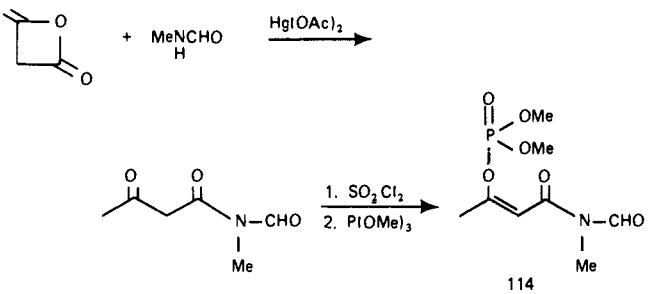
SCHEME XLIX



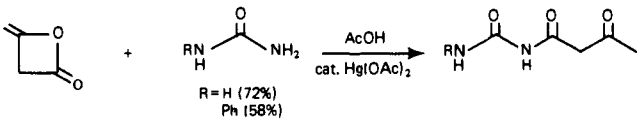
SCHEME L



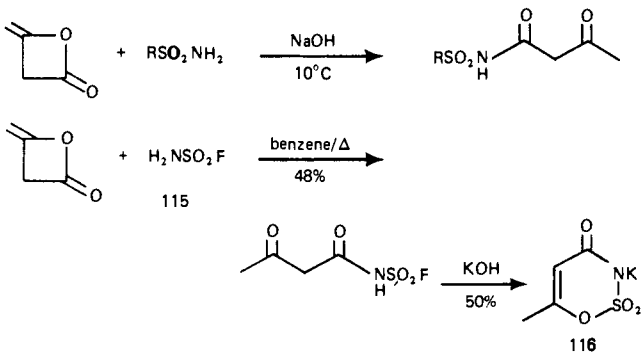
SCHEME LI



SCHEME LII



SCHEME LIII



acetylations of alkenes and aromatic compounds. The acetoacetylation of olefins with diketene is catalyzed by H_2SO_4, BF_3, or $ZnCl_2$.[212] Both benzene[17] and the three xylene isomers[213] have been acetoacetylated with diketene in the presence of 2 equiv of aluminum trichloride (Scheme LX).

Many acetoacetylations of aromatic rings are run with diketene in hydrogen fluoride, in which acetoacetyl fluoride (22) is the actual acetoacetylating reagent (see section II.D). Acetoacetylated aromatics have been used for the preparation of dyes,[56b] for chelation with metals,[214] and for the preparation of a prodrug based on acetoacetylated polystyrene.[215] The C-acetoacetylation of active methylene groups is readily accomplished with diketene and a variety of bases and is discussed in sections IV.A and IV.B.

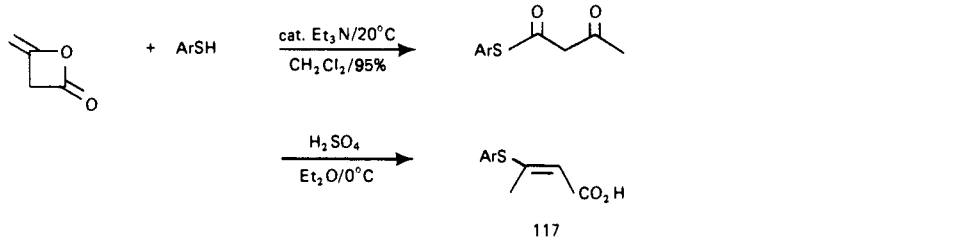
H. Acetoacetylation as Applied to Polymer Chemistry

Diketene is attractive to the polymer industry because it rapidly acetoacetylates even very hindered nucleophiles, such as those found in polymers, and because it produces dramatic changes in the physical properties of the compounds that result from this acetoacetylation.

The acetoacetylation of cellulose and cotton was first described in 1937.[216] Further research showed that cellulose triacetoacetate could be specifically prepared[217] and that cellulose was extensively acetoacetylated after 8 h at 60 °C in 10% diketene/1% H_2SO_4/AcOH.[218] Although cotton is not readily acetoacetylated when mixed with diketene, even in the presence of a catalyst, it is quickly acetoacetylated in hexane/benzene.[219] The resulting derivatized cotton is easily dyed by coupling with diazonium salts. Wool can also be acetoacetylated and then coupled with a diazonium salt to provide a colorfast, yellow fiber.[220] Other fibers with good light-fast and wash-fast colors have been similarly prepared.[221]

Corn starch[222] and wood[223] have been acetoacetylated with diketene. The free amino groups of aminoalkylated silica gels can be acetoacetylated to provide

SCHEME LIV



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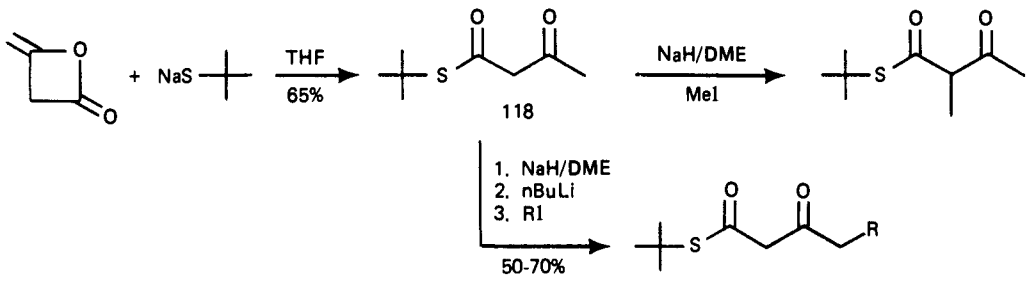
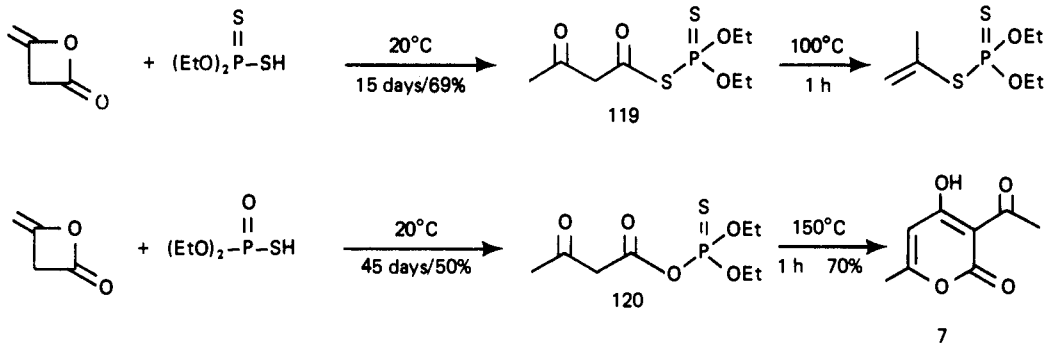
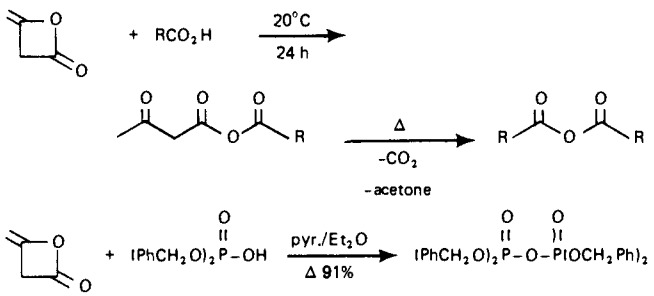


SCHEME LVI



SCHEME LVII

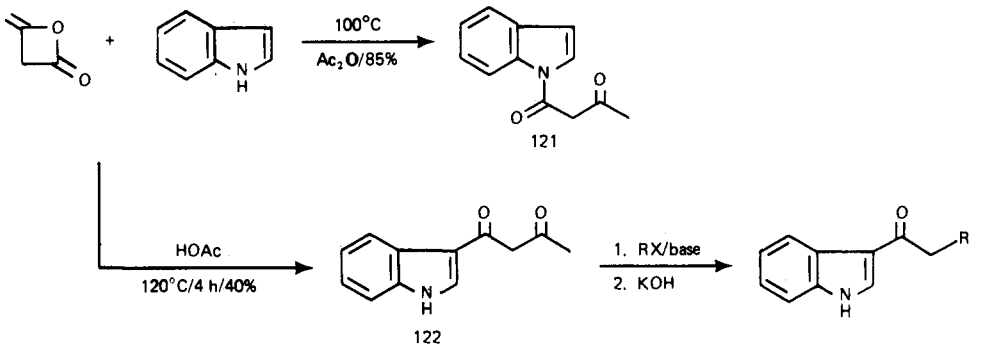


an immobilized chelating support;[224] some of these supports have been used for reverse-phase high-pressure liquid chromatography.[224a] Silica gel itself has been modified with diketene and then used as an ion-exchange resin for uranium.[225]

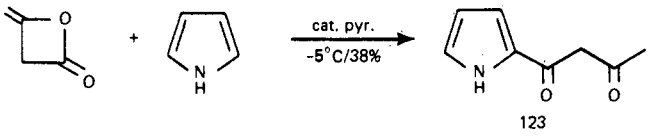
Many synthetic polymers have been modified with diketene, either before, during, or after polymerization. Poly(vinyl alcohol) can be treated with diketene to provide a poly(vinyl alcohol)/poly(vinyl acetoacetate) copolymer.[226] The modified polymer, frequently 3–6 mol % acetoacetate, is water resistant and resembles poly(vinyl acetate) in its ability to be molded into clear plastic films.[227] Poly(vinyl acetoacetate) is more stable and has better solubility properties than poly(vinyl alcohol).[228] Poly(vinyl acetoacetate) can be coupled with the diazonium salt derived from 4-aminosalicylic acid to afford a polymeric prodrug, which is claimed to release 4-aminosalicylic acid in the lower bowel.[215]

Several polyfunctional polymers,[229] such as poly(vinyl chloride)-*co*-poly(vinyl alcohol), have been acetoacetylated with diketene.[230] Following acetoacetylation, mixtures of gelatin and poly(vinyl alcohol) are miscible in all proportions and can be used to prepare photographic emulsions.[231] Other polymers that contain residual hydroxyl groups, such as polyesters,[232] epoxide-derived polymers,[233] and polymers containing bisphenol A,[234] have been acetoacetylated to provide products with improved physical properties. Similarly, polymers containing residual amino groups, such as polyurethanes[235] and polyamides,[236] have been stabilized via

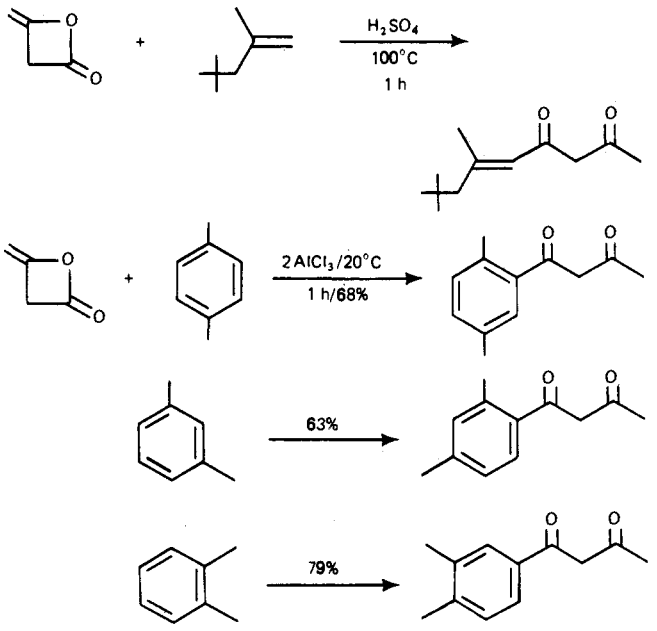
SCHEME LVIII



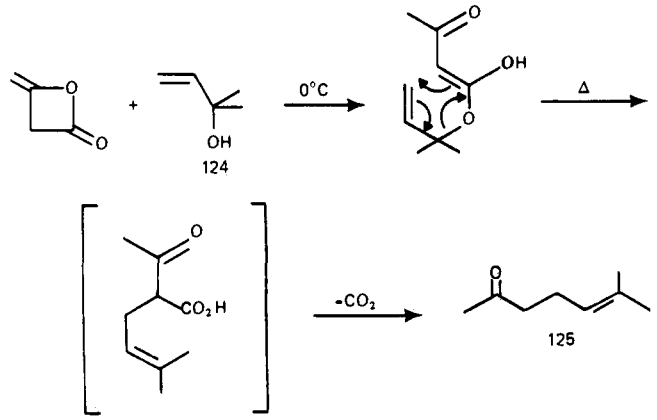
SCHEME LIX



SCHEME LX



SCHEME LXI



acetoacetylation with diketene; one such acetoacetylated polymer can be used for setting hair.[237]

Polymers with pendant acetoacetyl groups can be cross-linked to provide thermoset materials. Cotton has been acetoacetylated and then cross-linked with α,ω-diaminoalkanes[238] via enamine formation. Many O-[239] and N-acetoacetylated[240] polymers have been cross-linked with formaldehyde or other aldehydes.[241]

A series of hydroxylated or aminated acrylate,[242] acrylamide,[243] and methacrylate[244] monomers have been acetoacetylated prior to polymerization. Many copolymers derived from such acetoacetylated monomers are used either in the preparation of gelatin substitutes for the photographic industry or in coatings applications. Other monomers acetoacetylated with diketene have been incorporated into copolymers.[245] Allylamine is acetoacetylated with diketene to give *N*-allylacetoacetamide, which can be polymerized with other monomers to afford copolymers with modified properties.[246]

The chelation of acetoacetylated polymers with metals provides a means of cross-linking polymers and of introducing metals into plastics. Hard films have been obtained from acetoacetylated polymers chelated with zinc, tin, lead, mercury, aluminum, titanium, zirconium, and beryllium compounds.[247] Calcium carbonate can be retained on paper that has been acetoacetylated with diketene.[248] Acetoacetylated polymers have been used as ion-exchange resins.[249] A polystyrene matrix was acetoacetylated on the aromatic ring with diketene and aluminum trichloride to provide an ion-exchange resin which was highly selective for Fe(III). Approximately one-third of the aromatic rings could be functionalized, which resulted in a functional group density of approximately 2.4 mequiv/g.[250]

A vanadium-chelated acetoacetate resin has been used to catalyze the formation of ϵ-caprolactam from cyclohexanone oxime.[251] Nylon 6 has been treated with diketene and chelated with calcium, zinc, cobalt, and aluminum compounds to give fibers with good antistatic properties.[252] Water-gelled explosives have been prepared from acetoacetylated polymers.[253]

Diketene is an effective cocatalyst for the Lewis acid catalyzed polymerization of tetrahydrofuran[254] and also acetoacetylates the termini of the product.[255] Diketene has been used as a cocatalyst in the organoaluminum-catalyzed polymerizations of trioxane[256] and in some low-temperature vinyl polymerizations.[257]

I. Carroll Rearrangement of Acetoacetates

The Carroll rearrangement[258] provides a versatile method for preparing a γ,δ-unsaturated methyl ketone from diketene and an allylic or propargylic alcohol. For

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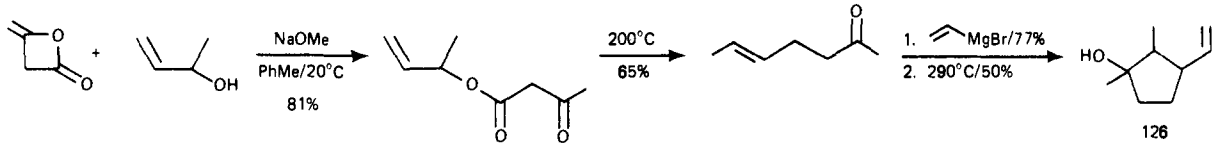
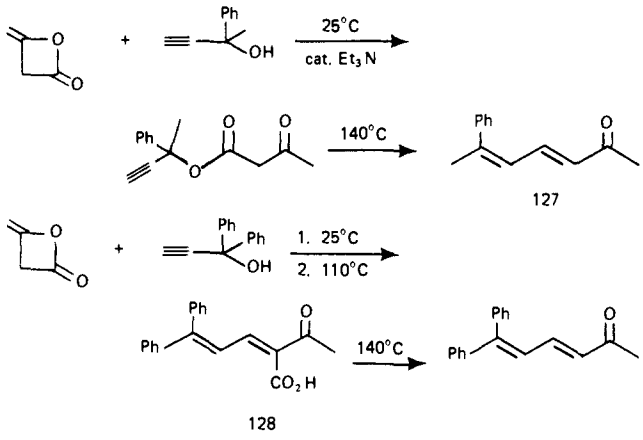


SCHEME LXIII



example, 2-methyl-3-buten-2-ol (**124**) can be treated with diketene, and the resulting acetoacetate can be pyrolyzed to provide 6-methyl-5-hepten-2-one (**125**)[259] (Scheme LXI); this rearrangement reaction is frequently run as a one-pot sequence.

The cyclopentanol **126**, used in an interesting but unsuccessful approach to pentalenolactone, was prepared via Carroll rearrangement of 3-butene-2-ol acetoacetate[260] (Scheme LXII).

Propargylic alcohol acetoacetates rearrange to afford conjugated dienones.[261] 6-Phenyl-3,5-heptadien-2-one (**127**) has the fragrance of wild strawberries and is used in perfumes and flavorants.[262] In the rearrangement of 1,1-diphenylpropynyl acetoacetate, a nondecarboxylated, primary rearrangement product (**128**) was isolated[263] (Scheme LXIII).

It is also possible to add diketene and an unsaturated alcohol, simultaneously but separately, to a high-boiling solvent that contains an amine catalyst and to isolate the rearranged product directly. In all cases, the Carroll rearrangement appears to be favored over olefin formation (see section III.A) during pyrolysis of the acetoacetate intermediates.

Aluminum isopropoxide catalyzes the Carroll rearrangement, and, in one example (**129** → **130**), a yield increase of 60% was realized by the addition of this catalyst[264] (Scheme LXIV). The Carroll reaction has been used to prepare a number of mono-,[261] di-, and trisubstituted olefins[265] and especially to prepare terpene and steroid derivatives which are important to the perfume and pharmaceutical industries, respectively.[266]

Geranylacetone (**131**) has been prepared from linalool (**132**) in 87% yield by the aluminum isopropoxide catalyzed Carroll rearrangement at 150 °C[267] (Scheme LXV). Farnesylacetone has been similarly prepared from nerolidol in 85% yield. Likewise, methylheptenone **125** (available by Carroll rearrangement) and acetylene can be reacted to provide dehydrolinalool (**133**), which provides pseudoionine (**134**) upon acetoacetylation and pyrolysis.[268]

Other perfume components have also been prepared by the Carroll reaction, including cyclic compounds such as **135**[269] and **136**[270] (Scheme LXVI).

The Carroll rearrangement has been used in a total synthesis of the sesquiterpene sinesal (**137**)[271] and in the preparation of dihydrojasmone (**138**),[272] thereby demonstrating the compatibility of the Carroll reaction with other functional groups (Scheme LXVII).

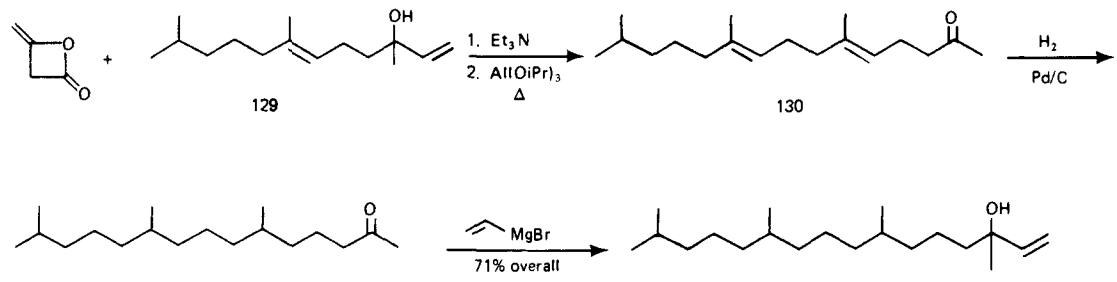
The synthesis of the sesquiterpene valerenal (**139**) is noteworthy for the mild reaction conditions used for the catalyzed Carroll reaction; a different product (**140**) was formed in the absence of the catalyst[273] (Scheme LXVIII).

The Carroll reaction has been used to prepare vitamin D_3 metabolites, as illustrated by the conversion of pregnenolone acetate into 25-hydroxycholesterol (**141**) in 25% overall yield[274] (Scheme LXIX).

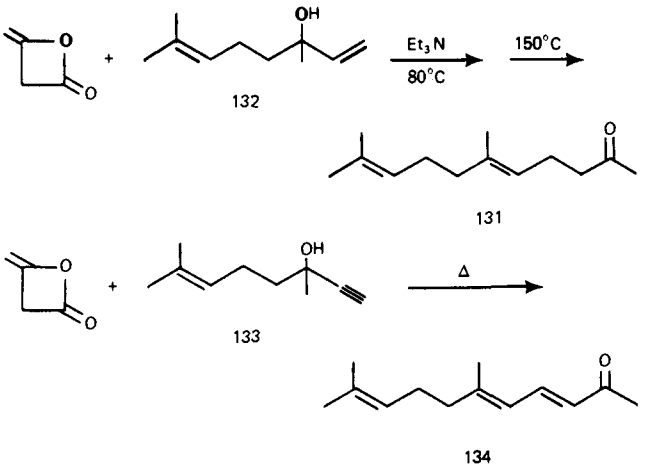
The ester enolate modification of the Carroll rearrangement has recently been described,[88] in which the dianions of allylic acetoacetates such as **142** were found to undergo Carroll rearrangement at low temperature. The intermediate acetoacetic acids **143** could be isolated and then quantitatively decarboxylated at 77 °C (Scheme LXX). The excellent yields obtained with this process, along with the mild reaction conditions, should greatly increase the versatility of the Carroll reaction.

Closely related to the aforementioned enolate modification of the Carroll rearrangement is the ester–enolate Claisen rearrangement of 2-butenyl 3-hydroxybutanoate esters.[275] Thus, (*E*)-2-buten-1-ol was treated sequentially with diketene and sodium borohydride to give ester **144** (Scheme LXXI). Upon

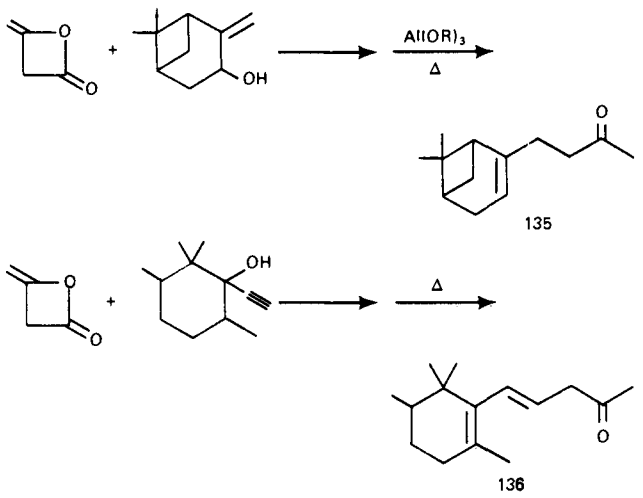
SCHEME LXIV



SCHEME LXV



SCHEME LXVI



treatment with 3 equiv of lithium hexamethyldisilazide, this ester (**144**) rearranged to give the hydroxy acid **145**, with good diastereoselectivity. Further variations of this reaction were examined.

IV. Six-Membered Heterocycles Derived from Diketene

Diketene contains both electrophilic and nucleophilic centers, enabling it to react with a large number of substrates to provide functionalized heterocycles. The majority of diketene chemistry is heterocyclic in nature.

A. Via C-Acetoacetylation

Heterocyclizations that involve diketene usually begin with acetoacetylation of a substrate, followed by an intramolecular condensation reaction. Normally, the initial acetoacetylation is effectively irreversible, while the ring-closure reaction is often an equilibrium process. As illustrated in the following sections, the type of ring system that will be formed can frequently be predicted on the basis of the initial position of acetoacetylation, while the exact substitution pattern of the nascent heterocycle is a function of the reaction conditions used (and hence the equilibria involved) during the ring-closure step.

When a substrate used for a heterocyclization reaction is initially acetoacetylated on carbon, the formation of a six-membered ring system containing one heteroatom can be expected. The simplest example of this type of reaction is the dimerization of diketene.

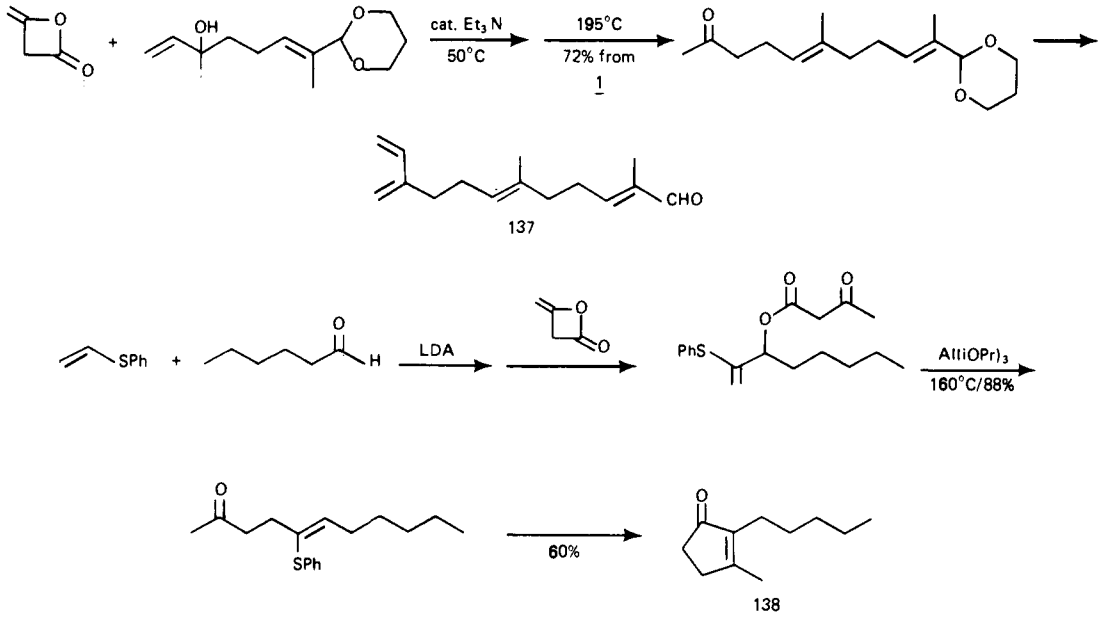
1. Diketene Dimerization

Diketene readily self-condenses to form dimers, oligomers, and polymers. The most common diketene dimer, dehydroacetic acid (DHA, **7**), and its sodium salt are important as fungicides and food preservatives.

At room temperature, diketene is very slowly converted into DHA upon standing, and DHA is frequently a byproduct of reactions involving diketene. Fortunately, DHA is easily removed from most reactions by either an aqueous bicarbonate wash or by precipitation.

Diketene can be deliberately converted into DHA with a variety of catalysts, and the reaction is rapid and exothermic. Thus, addition of diketene to a solution

SCHEME LXVII



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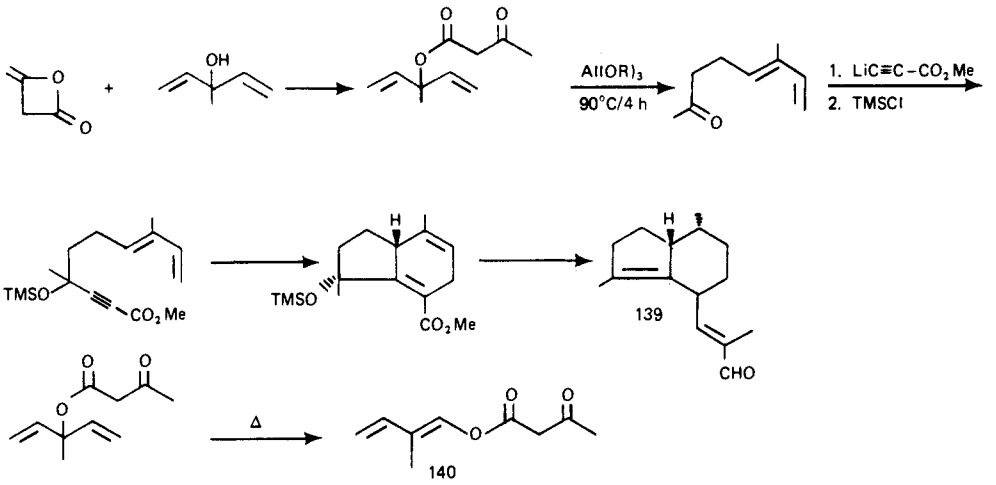

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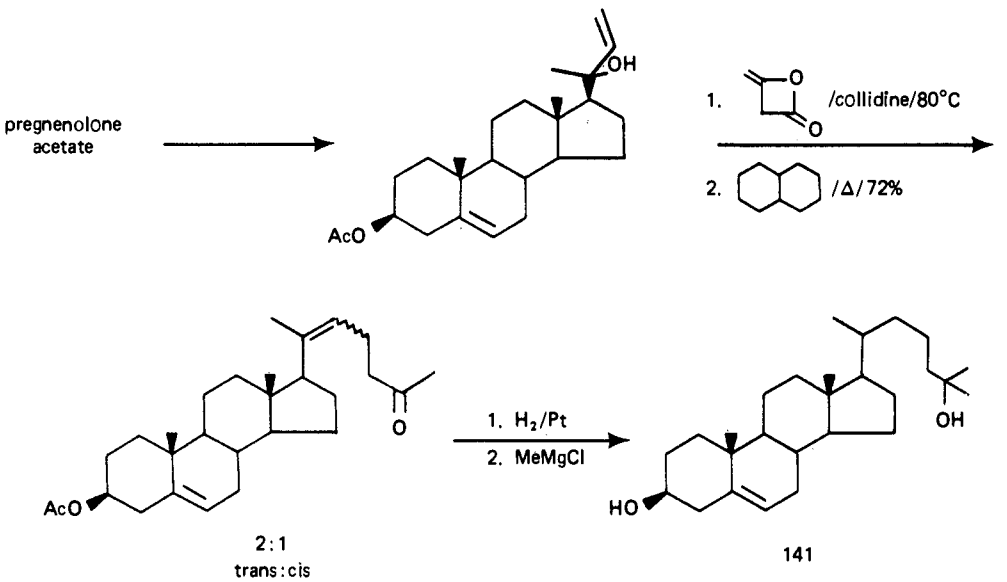

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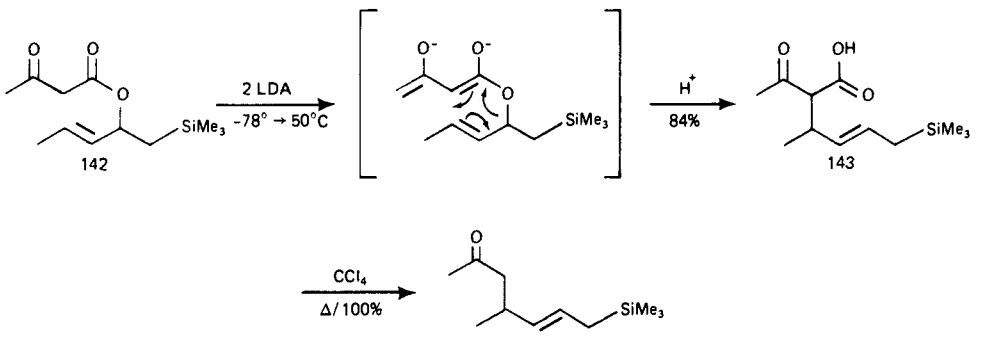
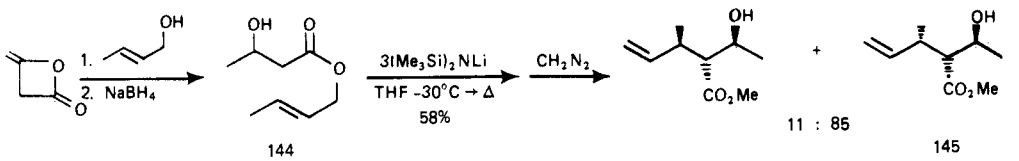


SCHEME LXXI



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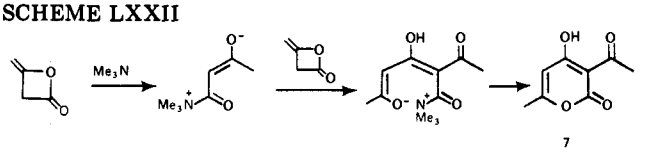
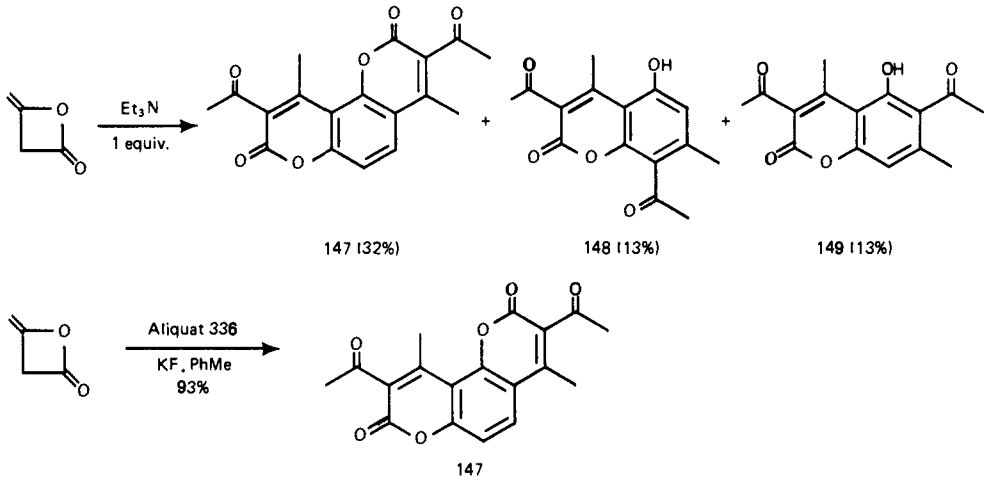
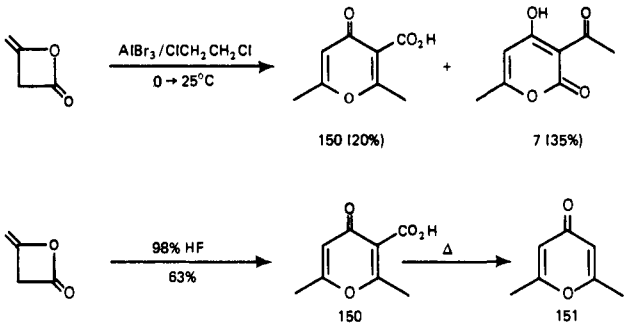


of benzene which contains a catalytic quantity of pyridine, followed by cooling, results in the precipitation of DHA from the reaction mixture.[9,276] Many other basic catalysts will also accelerate this dimerization; these catalysts include sodium acetate,[277] potassium

SCHEME LXXIII



SCHEME LXXIV



sorbate,[278] sodium alkoxides,[278] phenoxides,[279] and imidazole.[280] Tertiary amines[281] are the catalysts most commonly used.

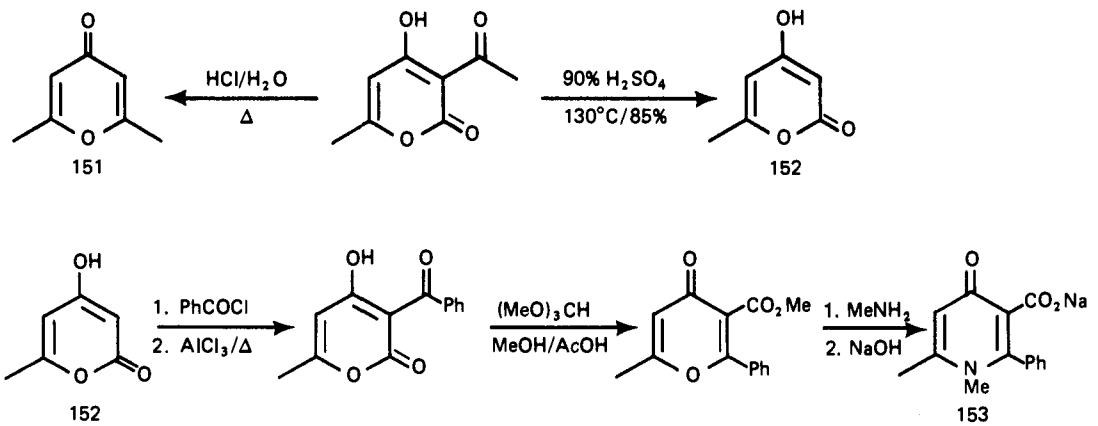
The catalytic activities of numerous tertiary amines in the preparation of DHA from diketene have been compared.[278] The catalyst of choice for industrial preparation of DHA from diketene appears to be diazabicyclo[2.2.2]octane (DABCO); under mild reaction conditions (40–50 °C, 15 min), DHA yields of over 95% have been realized by using DABCO as the catalyst.[282,283] Hydroxylated phenols, which also catalyze DHA formation,[284] have sometimes been used as cocatalysts.[283]

The role of the catalyst in this dimerization reaction is the activation of a molecule of diketene, such that it is rapidly C-acetoacetylated by another diketene molecule. The tertiary amine then becomes the leaving group for ring closure (Scheme LXXII).

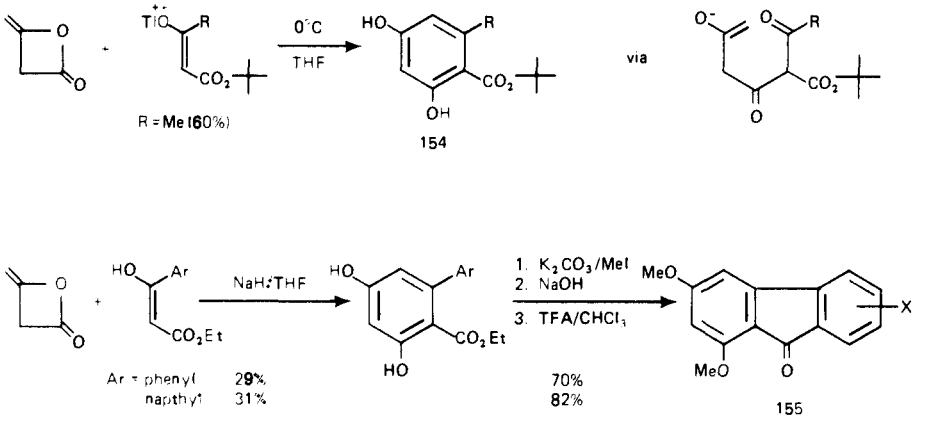
Although catalytic amounts of a tertiary amine accelerate DHA formation, the use of a stoichiometric quantity of a tertiary amine results in the formation of compounds which are produced from further condensation, such as **147–149**[285] (Scheme LXXIII). The first of these compounds (**147**) is readily separated from **148** and **149**, and all are reported to be useful indicators for acid–base titrations.[286] The use of a strongly basic ion-exchange resin as a catalyst for the self-condensation of diketene resulted in the formation of **147** in excellent yield.[193] Like DHA, **147** can sometimes be found as an insoluble byproduct of diketene reactions.

Lewis acids have also been used to effect the self-condensation of diketene. Anhydrous magnesium iodide is reported to efficiently promote the formation of DHA from diketene,[287] but it appears to be unique among the Lewis acids in this respect; the use of aluminum tribromide results in the formation of a mixture of DHA and 3-carboxy-2,6-dimethyl-4-pyrone (**150**)[288] (Scheme LXXIV). Compound **150** undergoes facile decarboxylation to give 2,6-dimethyl-4-pyrone (**151**), a product which can also be prepared by the high-temperature self-condensation of diketene under acidic conditions; the decarboxylation of **150** shifts the DHA/4-pyrone equilibrium to provide the 4-pyrone. The reaction of diketene with 98% hydrogen fluoride also gave a 63% yield of 3-carboxy-2,6-dimethyl-4-

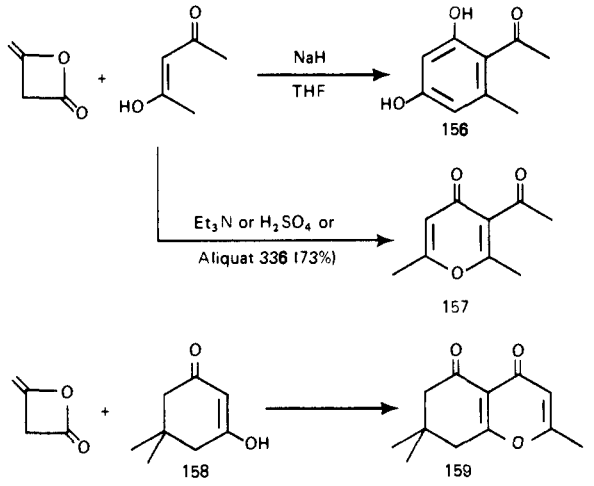
SCHEME LXXV



SCHEME LXXVI



SCHEME LXXVII



pyrone (150), along with a small amount of DHA, via dimerization of acetoacetyl fluoride.[289]

Pyrone 151 can also be prepared in excellent yield by refluxing DHA in aqueous acid, while the action of concentrated sulfuric acid on DHA gives 4-hydroxy-6-methyl-2-pyrone (152)[290] (Scheme LXXV). This latter pyrone (152) can be used for the preparation of a plant growth regulator, 153.[291]

The polymerization of diketene is discussed in section VI.C.

2. β-Dicarbonyl Compounds

Active methylene groups can be acetoacetylated with diketene, and the enolates of the resulting products can be used as the nucleophiles in intramolecular condensations. Thus, the sodium salts of β-keto esters were found to react with diketene to provide orsellinate esters such as 154[292] (Scheme LXXVI). Subsequent modifications of this latter procedure, including the use of thallium(I) salts of *tert*-butyl acetoacetate esters, gave greatly improved yields.[293] This condensation reaction has been extended to provide a route to 1,3-dimethoxyfluorenones (e.g., 155)[294] and to 5-substituted resorcinols.[292] The use of a strong base for the reaction of diketene and active methylene compounds appears to favor the mode of ring closure in which cyclization occurs via the unconjugated enolate and results in carbon–carbon bond formation.

Resorcinols (156) are also formed in the reaction of β-diketones with diketene and a strong base, while 4-pyrones (e.g., 157) result from the use of triethylamine,[295] Aliquat 336,[193] or sulfuric acid[296] as the catalyst (Scheme LXXVII). However, even in the presence of a strong base, dimedone (158) gives a 4-pyrone (159).[295]

Sodium diethylmalonate and diketene combine to give 3-carboethoxy-4-hydroxy-6-methyl-2-pyrone (160), which can be decarboethoxylated via the free acid 161.[297] This 3-carboxy-2-pyrone (161) is more conveniently accessed via the acid-catalyzed decomposition of 5-acetoacetyl-2,2-dimethyl-4,6-dioxo-1,3-dioxane (162), which can be prepared from diketene and Meldrum's acid[298] (Scheme LXXVIII).

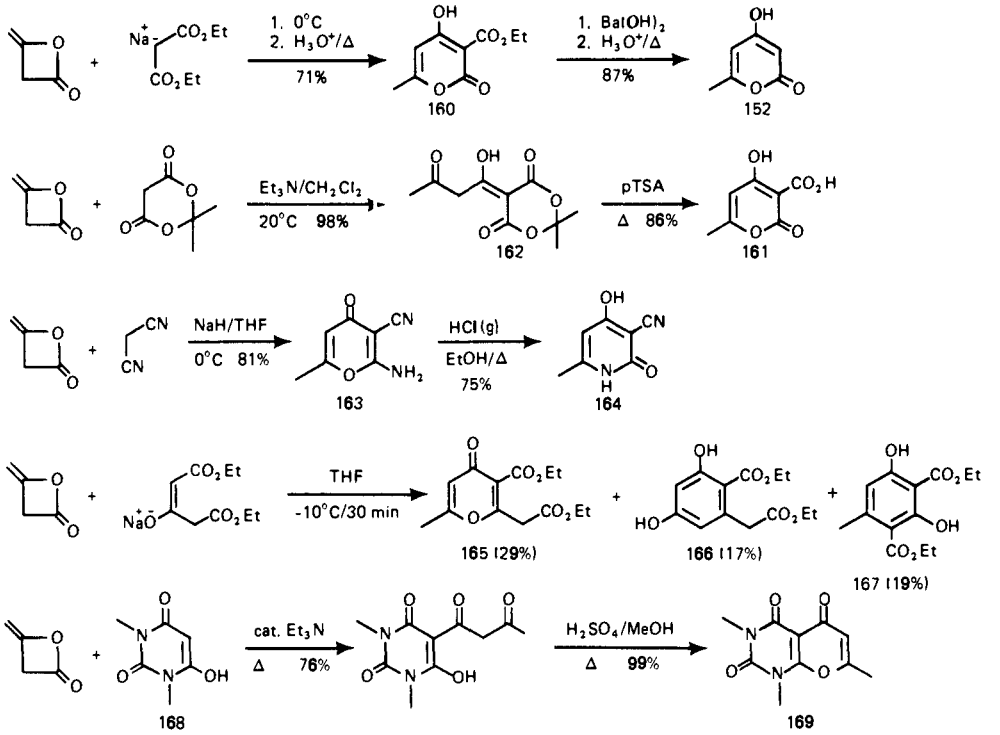
Diketene reacts with malononitrile and other malonate derivatives to form pyrones (163) and pyridones (164).[299,300] Condensation of diketene with sodium diethyl acetonedicarboxylate gave a mixture of the diester 165 and the substituted resorcinols 166 and 167;[301] the use of the corresponding magnesium enolate altered the product ratios but did not improve the yields.[301b] 1,3-Dimethylbarbituric acid (168) has been acetoacetylated with diketene in the presence of triethylamine; the resulting acetoacetate was converted into pyranopyrimidine 169.[302] Based upon the aforementioned reactions of diketene and compounds bearing active methylene groups, it appears that the use of a weak base, such as triethylamine, favors the formation of C-acetoacetylated, noncyclized adducts. These adducts readily cyclize, oftentimes in situ, under more forcing conditions (stronger base, heat, acidic catalyst).

B. Via C-Acetoacetylation of Nitrogen-Containing Compounds

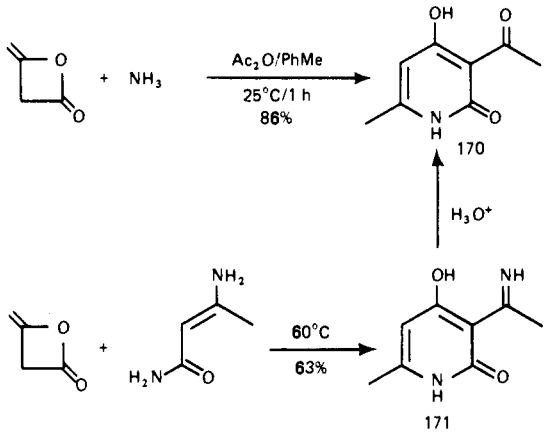
1. Acetoacetamides and β-Aminocrotonates

Diketene self-condenses in the presence of amines to provide pyridones, in a manner analogous to the preparation of pyrones from diketene. As before, the reaction proceeds by acetoacetylation on carbon. Thus, 2 equiv of diketene and ammonia combine at 20 °C to give 3-acetyl-4-hydroxy-6-methyl-2-pyridone (170) in excellent yield (Scheme LXXIX), presumably by acetoacetylation of the active methylene group of acetoacetamide (acetoacetamide formation is faster than diketene dimerization.[303,304] The reaction of diketene with 3-aminocrotonamide results in the formation of the imino analogue (171) of 170.[305]

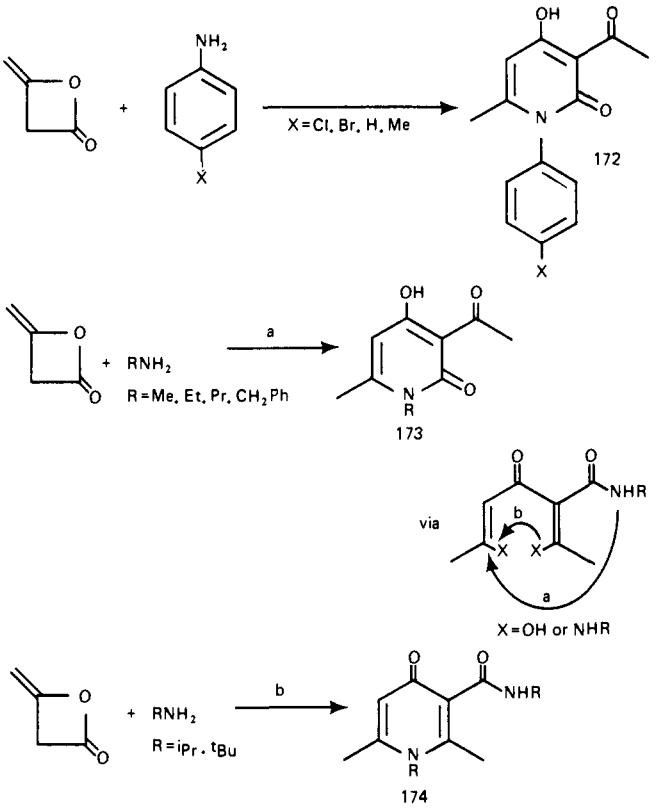
SCHEME LXXVIII



SCHEME LXXIX



SCHEME LXXX



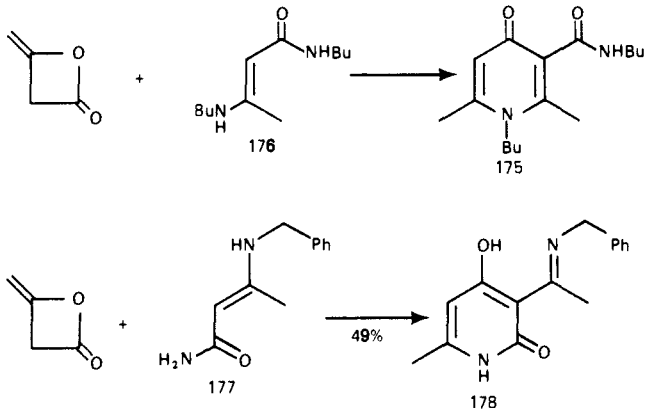
The action of diketene on anilines affords 1-aryl-2-pyridones, such as **172** (Scheme LXXX). Several of these pyridones exhibit fungicidal activity.[306] Unhindered, primary aliphatic amines react with 2 equiv of diketene to give 2-pyridones **173**, which can also be obtained by reacting 1 equiv of diketene with an *N*-alkylacetoacetamide. Sterically hindered aliphatic amines, however, give 4-pyridones (**174**); presumably ring closure through the hindered amide nitrogen (path a) becomes slower than enamine formation and subsequent Michael addition (path b).[304]

This explanation of 2-pyridone vs. 4-pyridone formation is consistent with the isolation of a 4-pyridone (**175**) from the reaction of diketene with *N,N'*-di-*n*-butyl-3-aminocrotonamide (**176**),[307] in which the amide nitrogen was hindered and the enamine was preformed (Scheme LXXXI). Also, the reaction of diketene and aminocrotonamide **177**, in which the enamine was preformed but the amide unhindered, provided the 2-pyridone **178**.[308]

An attempted acetoacetylation of glycine (and other amino acids) with excess diketene in aqueous sodium hydroxide resulted in the formation of the 1-substituted 2-pyridones (e.g., **179**), as well as *N*-acetoacetylglycine (Scheme LXXXII). The structure of the product was confirmed via deacetylation to a known compound (**180**).[309] Treatment of dehydroacetic acid with glycine provided the isomeric structure **181**.[310]

Under conditions conducive to acetoacetylation of amides, excess diketene reacts with amides to form

SCHEME LXXXI



1-acyl-2-pyridones (182)[193] (Scheme LXXXIII). In this reaction, the methylene group of the initially formed acetoacetimide is acetoacetylated, followed by intramolecular ring closure.

N,N-diacetoacetylamines can be made from acetoacetamides and diketene in the presence of weak bases, such as N,N-disubstituted anilines, thus making another type of 2-pyridone (183) available from diketene[311] (Scheme LXXXIV).

The self-condensation of acetoacetarylides under acidic conditions provides 4-pyridones (Scheme LXXXV),[307] some of which (184) have antiinflammatory activity.[312] The self-condensation of two *N*-alkylacetoacetamides under acidic conditions, however, gives yet another 2-pyridone derivative (185); small quantities of the isomeric product 186 are sometimes formed.[313] Both 185 and 186 are formed via an enamide intermediate; 185 results from ring closure through the conjugated α,β-enamide, while 186 was formed by cyclization of the unconjugated enamide.[307,313]

The reaction of 3-aminocrotonates with diketene affords 4-pyridones such as 187,[314] which have been further converted into fused heterocyclic systems[315] (Scheme LXXXVI); 3-aminocrotononitriles and cinnamonitriles also react with diketene to provide 4-pyridones, such as 188. These heterocyclizations begin with a C-acetoacetylation typical of an enamine, but because the enamine nitrogen atoms were not derived from a secondary amine, the nitrogen atom can cyclize on the acetoacetylated intermediate to provide a pyridone.[314]

3-Alkylamino and 3-arylaminocrotonates react with diketene to give 1-substituted 4-pyridones (189)[316,317] (Scheme LXXXVII). A number of related compounds, such as 4-(methylamino)-3-penten-2-one, also react with diketene to furnish 4-pyridones.[317] Several plant growth regulators, such as 190, are prepared from 3-aryl-3-aminopropenoate esters and diketene.[291] The reaction of enamido esters and diketene has been extended to the preparation of pyranopyrimidines 191 from aminouracils (see compound 169 for comparison).[318]

2-Pyridylacetonitrile reacts with diketene in a manner similar to aminocrotonates and produces the fused, bicyclic 4-pyridone 192[319] (Scheme LXXXVIII). An intermediate C-acetoacetylated adduct can be isolated.

2. Enamines, Ynamines, and Ketene Acetals

Diketene reacts with enamines to provide six-membered heterocycles containing one ring heteroatom, as would be expected from an initial acetoacetylation on carbon (Scheme LXXXIX). These reactions are frequently described as cycloaddition reactions even though polar intermediates are involved. In part, this description is used because acetylketene has been considered as an intermediate in uncatalyzed, thermal heterocyclization reactions of diketene.

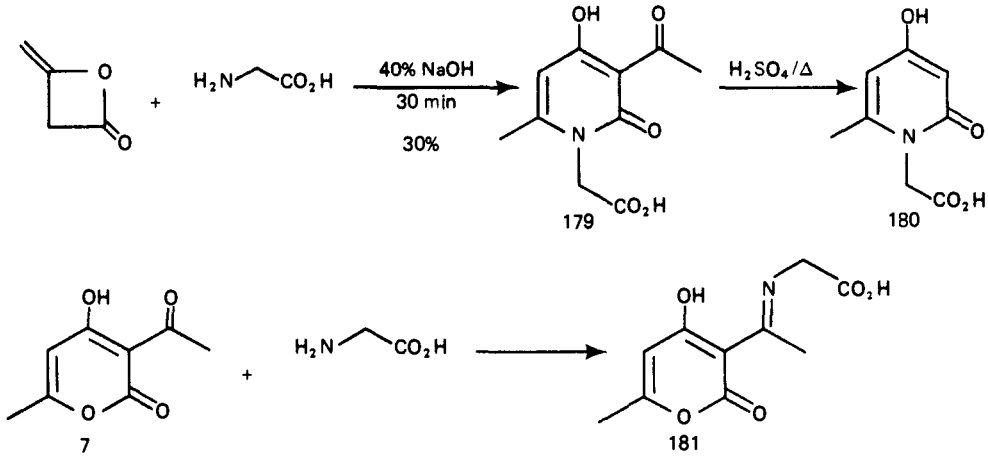
The reaction of diketene with enamines derived from secondary amines gives 4-pyrones that no longer contain nitrogen. These cycloalkylpyrones (e.g., 193) can be interconverted between their ring-opened (194) and ring-closed forms, and they are also smoothly converted into 4-pyridones (195)[320] (Scheme XC).

The reaction of diketene with enamines has been used in the preparation of 7,8-dihydro-2,6-dimethylchromone (196)[321] and in a two-step synthesis of the alkaloid isobellendine (198)[322] (Scheme XCI).

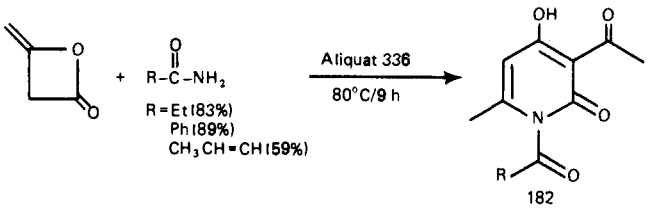
In the presence of triethanolamine, enaminones 199 and diketene combine to provide 5,6-unsubstituted 2-pyridones 200 via an anomalous N-acetoacetylation of the enaminone (Scheme XCII); this may be a result of the basic reaction conditions.[323] As noted previously, pyridone formation can be expected from the reaction of diketene and enamines that were not derived from secondary amines.

Also, unlike most other imines (see section IV.D), *N*-aryl imines (e.g., 201, 202) react with diketene as the enamine and provide 4-pyridones (e.g., 203)[324] (Scheme

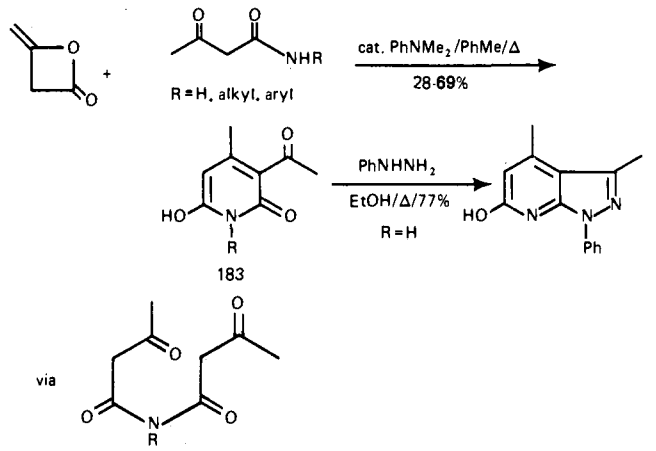
SCHEME LXXXII



SCHEME LXXXIII



SCHEME LXXXIV



XCIII). 1-Methyl-3,4-dihydroisoquinoline is another imine that reacts with diketene at carbon, in an enamine-like manner, to give the fused 4-pyridone **204**.[325]

The action of ynamines on diketene provides products (**205**) in which the nitrogenous functionality is retained (Scheme XCIV); these adducts have been converted into various other compounds.[326]

Ketene acetals and their congeners undergo polar cycloaddition reactions with diketene to afford substituted 4-pyrones such as **206**[327] (Scheme XCV). In one case, an orthoester intermediate (**207**) was isolated.[327b] Although yields are generally low, this process is quite general, and a large number of different substituents can be introduced into the product pyrones.

C. Hantzsch Pyridine Synthesis

An important reaction involving diketene derivatives provides yet another series of substituted pyridines. The Hantzsch pyridine synthesis is a preparation of 1,4-dihydropyridines (e.g., **208**) from ammonia (or a primary amine), an aldehyde, and a β-keto ester or a related derivative[328] (Scheme XCVI). Symmetrical 1,4-dihydropyridines are easily prepared by mixing (cautiously) the three reagents.

Unsymmetrical Hantzsch dihydropyridines are best prepared by condensation of a 3-aminocrotonate ester (e.g., **209**) with a 2-alkylidene acetoacetate ester (e.g., **210**)[329] (Scheme XCVII). Many dihydropyridines, such as nifedipine (**211**),[330] nimodipine (**212**),[331] and nicardipine (**213**),[332] act as vasodilators and antihypertensives.[333] This area of medicinal chemistry is quite active, and many analogous 1,4-dihydropyridines have recently been patented.[334]

Dihydropyridines without a 4-substituent can be prepared by using formaldehyde or hexamethylenetetramine in the Hantzsch reaction[132] (Scheme XCVIII); some of these dihydropyridines (e.g., **215**) have been shown to be effective against Walker's carcinoma.[335] Both alkyl and aryl esters of 4-unsubstituted dihydropyridines can be used as antioxidants (**216**), as they are readily oxidized to pyridines under a variety of conditions.[132] The preparation of pyridines from 1,4-dihydropyridines, via the Hantzsch synthesis, has been used in the total synthesis of the alkaloid clivimine (**217**).[336]

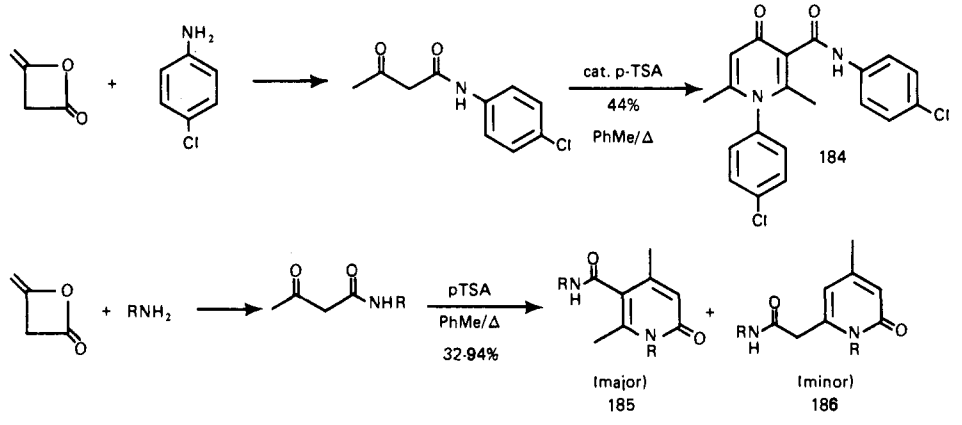
D. Via N-Acetoacetylation of Polarized Multiple Bonds

Another major type of heterocyclization that involves diketene is that in which diketene initially N-acetoacetylates a substrate containing a C–N multiple bond. The expected product from this type of reaction is a six-membered ring containing two heteroatoms.

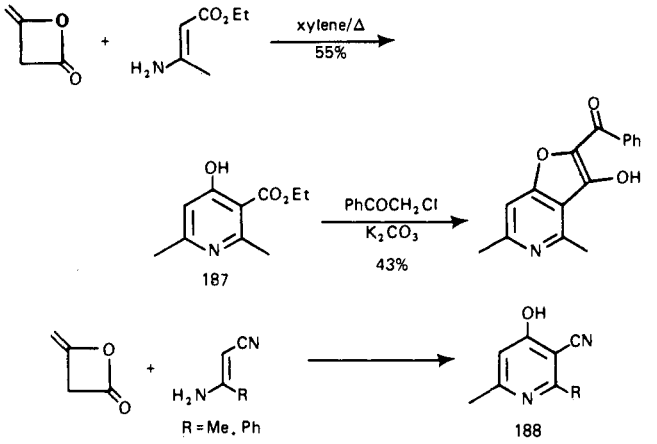
Imines unsubstituted on nitrogen react with diketene to afford 1,3-oxazin-4-ones such as **218**[337] (Scheme XCIX). Under basic conditions, N-substituted imines also react with diketene to afford 1,3-oxazinones.[338] Thus, the action of diketene on diazepam (**219**) provides the tranquilizer ketazolam (**220**) in excellent yield.[338b]

The reactions of N-substituted imines with diketene under neutral conditions are more complex, and the reaction products are not obviously predictable. Thus, diketene slowly reacts with benzylidene imines such as **221** to afford acetoacetamides (e.g., **222**)[337a,339] (Scheme C). A β-lactam intermediate has been postulated for these reactions,[339] but the lengthy reaction times and the low yields make it difficult to eliminate other re-

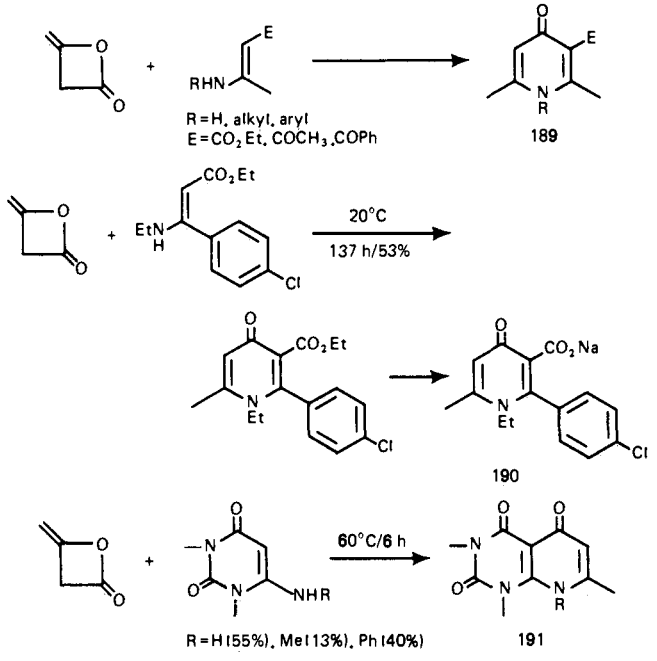
SCHEME LXXXV



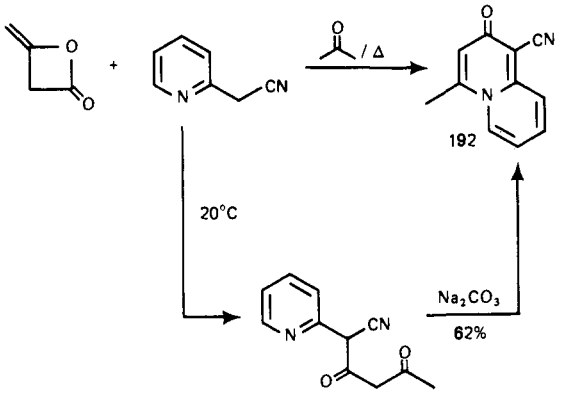
SCHEME LXXXVI



SCHEME LXXXVII



SCHEME LXXXVIII



action pathways, such as dissociation of the imine. In the case of ethylidene imine **223**, the more complex products **224** and **225** were formed.[340]

Cyclopentylideneaniline reacts with diketene under acidic conditions as an enamine, as was discussed in section IV.B. Moderate yields of the 1,3-oxazin-4-ones **227** are slowly formed from diketene and *N*-acyl imines **226**[341] (Scheme CI).

Diketene reacts with ethyl benzimidate and ethyl phenacetimidate to give oxazinones (e.g. **228**) via isolable intermediate 2-ethoxy-1,3-oxazin-4-ones[342] (Scheme CII); imidate esters of pyridinecarboxylic acids react similarly.[343] Oxazinone **228** has been converted into several highly functionalized pyridones,[342] into an hydroxypyrimidine,[344] and into 1,2,4-triazole **229**.[345] The related reaction of ribofuranosyl formimidates has been used to prepare C-nucleosides.[346]

The interaction of diketene, ethyl isobutyrimidate, and ammonia provides 4-hydroxypyrimidine **230**, which is known as Oxy-P[347] (Scheme CIII). This compound is widely used in the manufacture of the insecticide Diazinon (**231**). Oxy-P has also been prepared from diketene and either isobutyramidine,[348] isobutyronitrile,[349] isobutyrate esters,[350] or isobutyramide;[351] overall yields were excellent. The synthesis of Oxy-P is an excellent demonstration of the versatility of diketene and its derivatives in heterocyclic synthesis, and also shows that diketene reactions can indeed provide excellent yields when properly utilized.

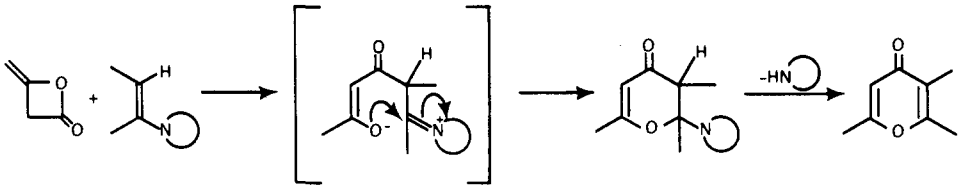
Kato determined that the reaction of excess diketene with *N*-alkylimino ethers in acetic acid produced the complex 1,6-napthyridine derivatives **232** and **233**[352] (Scheme CIV). However, equimolar quantities of diketene and 2-methoxy-1-pyrroline combined under neutral conditions (0 °C, no solvent) to afford pyrrolooxazinone **234** as the major product;[353] the isomeric product **235** was formed from larger cyclic imino ethers.

A number of hydroxypyrimidines have been prepared from diketene and aliphatic or aromatic amidines;[354] N-alkylated benzamidines are normally acylated on the substituted nitrogen atom[355] (Scheme CV). Diketene reacted with the amidine functionality of benzodiazocene **236** under mild conditions to afford a mixture of adducts **237** and **238**, which were readily converted into isomeric pyrimidodiazocenes[356] (Scheme CVI). A facile 1,3-isomerization of the acetoacetyl group was observed if compound **238** was heated, resulting in the formation of **239**. The reaction of diketene and the benzodiazepine analogous to **236** afforded predominantly the acetoacetamidine.[356]

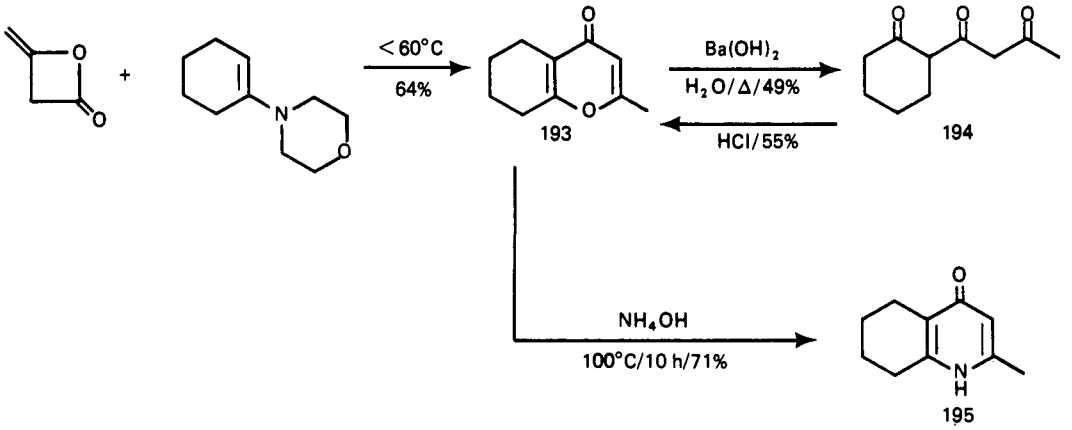
Under basic conditions, guanidine reacts with diketene to give 2-amino-4-hydroxy-6-methylpyrimidine (**240**);[354] biguanide reacts under neutral conditions to afford 2-guanidino-4-hydroxy-6-methylpyrimidine[357] (Scheme CVII). Treatment of bis guanidine **241** with diketene provided a mixture of hydroxypyrimidine **242** and triazine **243**.[357,358] Diketene and *N,N'*-diphenylguanidine combine under neutral conditions to give an isolable orthocarbamate intermediate, which is converted into pyrimidone **244** upon acidification.[359]

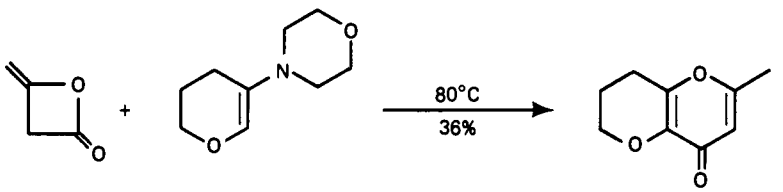
Diketene reacts with cyanamide and substituted cyanamides at 25 °C to give 1,3-oxazine-4-ones **245**[326,360] (Scheme CVIII). These 2-aminooxazinones isomerize to their 2-imino isomers upon heating and may be rearranged into 1-substituted uracils (**246**) following treatment with acetic acid at reflux.[360] A trace (5%) of a 3-substituted uracil was isolated from an attempt to effect this latter rearrangement in dilute HCl.[361] Disubstituted cyanamides and acyl cyanamides react similarly, and the chemistry of the resulting heterocycles has been studied.[362] Diketene also combines with isocyanic acid to produce an oxazinedione (**247**),[361,362] that has been efficiently converted into both uracil **248**

SCHEME LXXXIX



SCHEME XC





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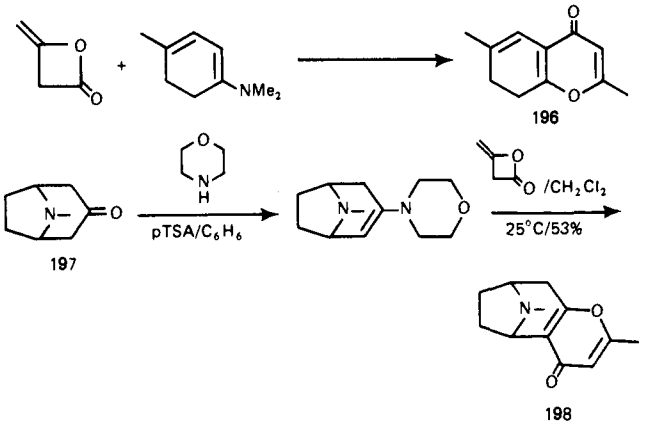
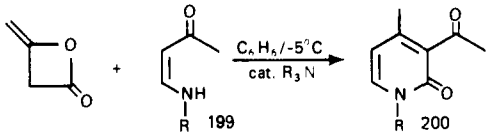
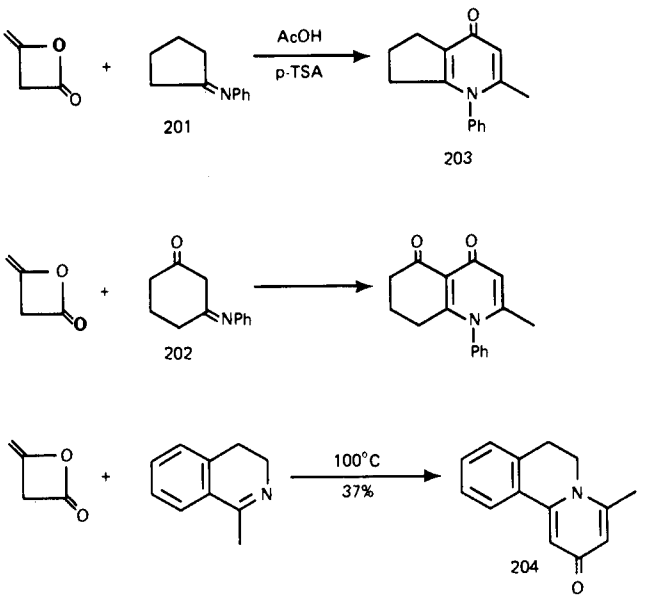


SCHEME XCII



R = H(53%), Me(46%), iPr(80%)

SCHEME XCIII

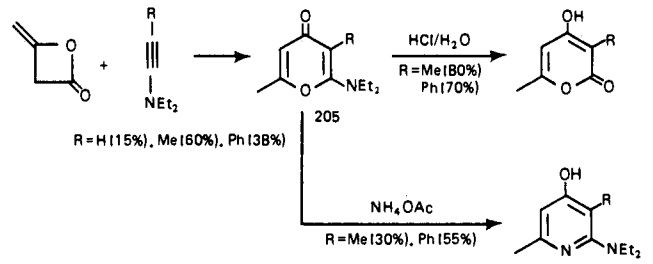


and pyrazolone **249**.[363] This latter paper is noteworthy for the in situ preparation of isocyanic acid from nitrourea.

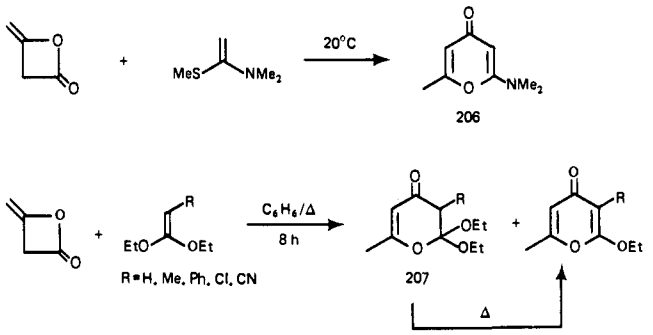
The reaction of ammonium thiocyanate with diketene provides a good yield of oxazinonethione **250**[361,364] (Scheme CIX). A series of 1,3-oxazinimines such as **251** has been prepared in excellent yield from carbodiimides and diketene (Scheme CX); the yields were markedly higher with lengthy, room-temperature reactions than with those run at reflux (benzene, 6 h).[365]

Diketene reacts with fluorosulfonyl isocyanate to afford *N*-(fluorosulfonyl)-1,3-oxazine-2,4-dione (**252**)[366] (Scheme CXI). This result is in marked contrast to the reaction of fluorosulfonyl isocyanate with *tert*-butyl acetoacetate, which provides an acetoacetamide precursor (**253**) to the artificial sweetener acesulfame K (**116**).[367]

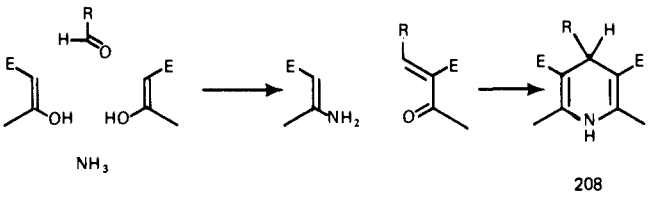
SCHEME XCIV



SCHEME XCV



SCHEME XCVI



The interaction of diketene and isothioureas (**254**, **255**) to afford 1,3-oxazine-2,4-dione derivatives is quite sensitive to the reaction conditions[359,368] (Scheme CXII). An intermediate adduct can be isolated from the 20 °C reaction of isothioureas and diketene; two different structures have been proposed for this intermediate.

E. Reactions with N-Heterocycles and Their *N*-Oxides

Diketene reacts readily with many nitrogen heterocycles to give discrete, fused polycyclic products. In the simplest example, pyridine combines with either ketene or diketene to afford the tricyclic system **256**, which is frequently referred to as Wollenberg's compound.[369] A plausible reaction mechanism is presented in Scheme CXIII.

The reactions of quinoline[370] and isoquinoline[371] with excess diketene in refluxing benzene have been studied. In the case of isoquinoline, lower reaction temperatures favored the O-acetoacetylation required to afford **257** (Scheme CXIV).

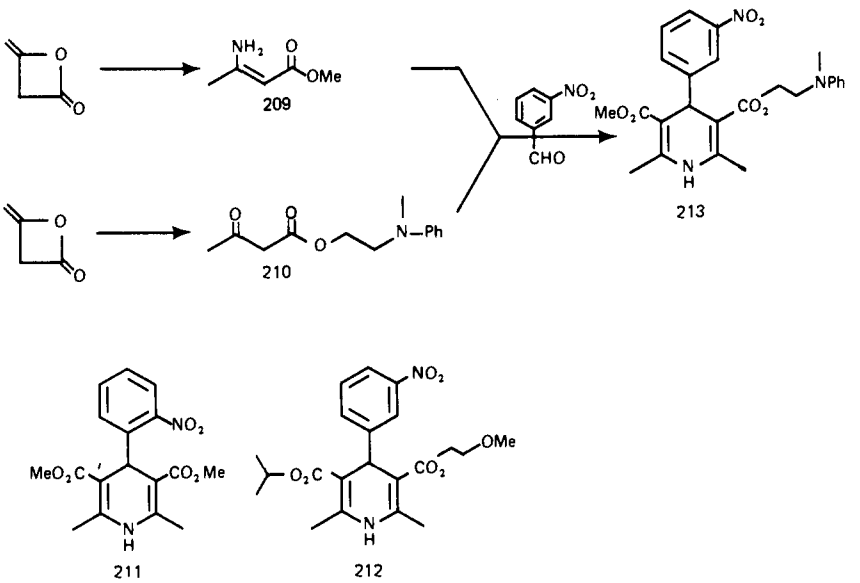
The proposed reaction mechanism for the formation of Wollenberg-type compounds is supported by the reaction of diketene and phenanthridine (**258**), in which a C-acetoacetylated intermediate (**259**) was isolated prior to conversion into the fused pyrone **260**[372] (Scheme CXV).

The action of diketene on isoquinolines in carboxylic acid media provides adducts **261**[373] (Scheme CXVI); phthalazine (**262**) and 2,5-naphthyridine react similarly, while quinoxaline fails to react. This reaction of an acid, diketene, and an isoquinoline appears to be similar to the Reissert reaction and has been suggested to proceed via a mixed acetoacetic anhydride.[373] Benzimidazole (**263**) reacts with diketene under acidic conditions to afford both the acetonylated adduct **264** and diketopiperidine **265**;[374] the acidic reaction conditions appear to inhibit the further conversion of **265** into a Wollenberg-type adduct. Acridine reacts slowly with diketene to afford a mixture of starting materials and 9-acridanylacetone **266**, presumably via an N-acetoacetylated, 9,10-bridged species such as **267**.[375]

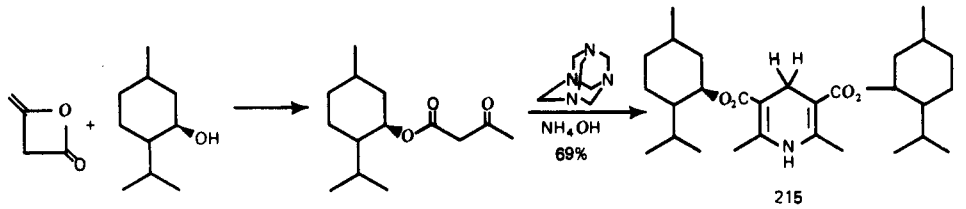
5-Phenyltetrazole is acetoaceylated with diketene at N-2, undergoes intramolecular cyclization via the amide oxygen and extrudes nitrogen to produce 1,3,4-oxadiazoles **268**; the byproduct **269** is the result of further condensation of **268** with diketene[376] (Scheme CXVII).

The reactions of heterocyclic *N*-oxides with diketene often provide products resulting from acetonylation α

SCHEME XCVII



SCHEME XCVIII



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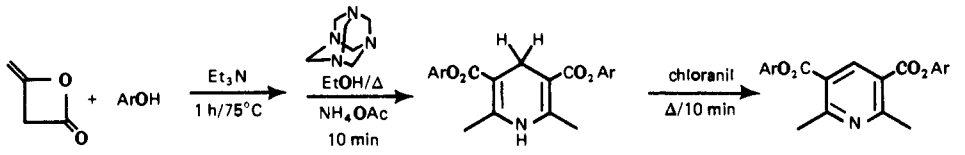
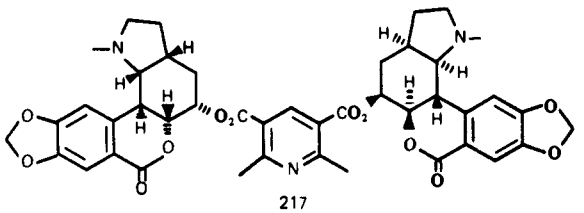
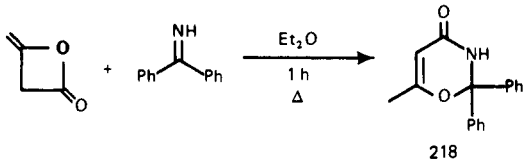




217

SCHEME XCIX



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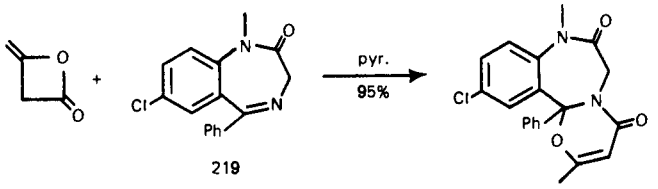
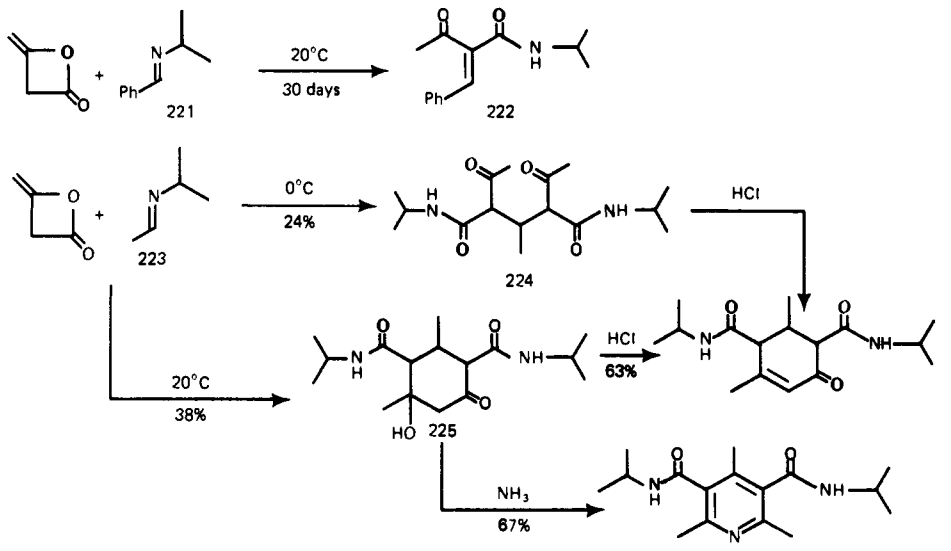


219 220

to the nitrogen atom. Diketene reacts with quinoline *N*-oxide (**270**) to afford pyrone **271**[377] and with isoquinoline *N*-oxide (**272**) to give several products which arise from a common acetonylated intermediate[378] (Scheme CXVIII). In the reaction of **270** with diketene, traces of intermediate **273** were isolated and were subsequently converted into quinolinylpyrone **271** in good yield.[377] This acetonylation is also observed in the reaction of acridine *N*-oxide (**274**) with diketene, in which a 9,10-bridged intermediate is clearly involved.[379]

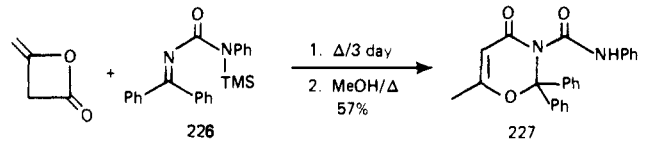
4-Aminopyridine *N*-oxide (**275**) only reacts with diketene in the presence of a base and gives a poor yield of pyrone **276** (Scheme CXIX). However, simple N-acetoacetylated products have been prepared from

SCHEME C

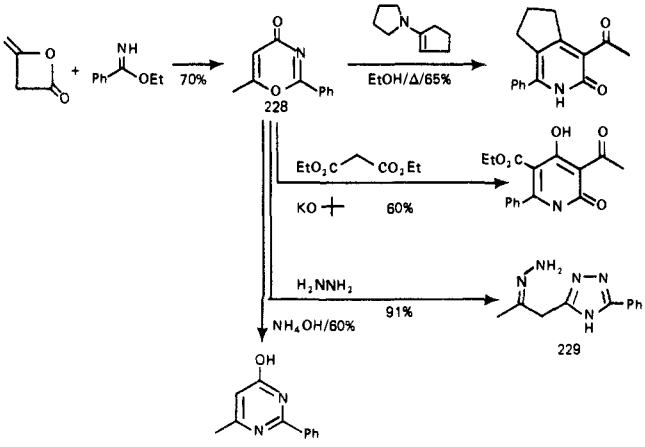


221 222 223 224 225

SCHEME CI



SCHEME CII



several substituted 4-aminopyridine *N*-oxides.[380] 2-Aminopyridine *N*-oxide can be acetoacetylated with 1 equiv of diketene to afford an 80% yield of a product which will react with additional diketene to produce pyrone **277**.[381]

A radical mechanism has been suggested to explain the products that result from the reaction of diketene and *N*,*N*-dimethylaniline *N*-oxide (**278**)[382] (Scheme CXX).

F. Reactions with Aminoheterocycles

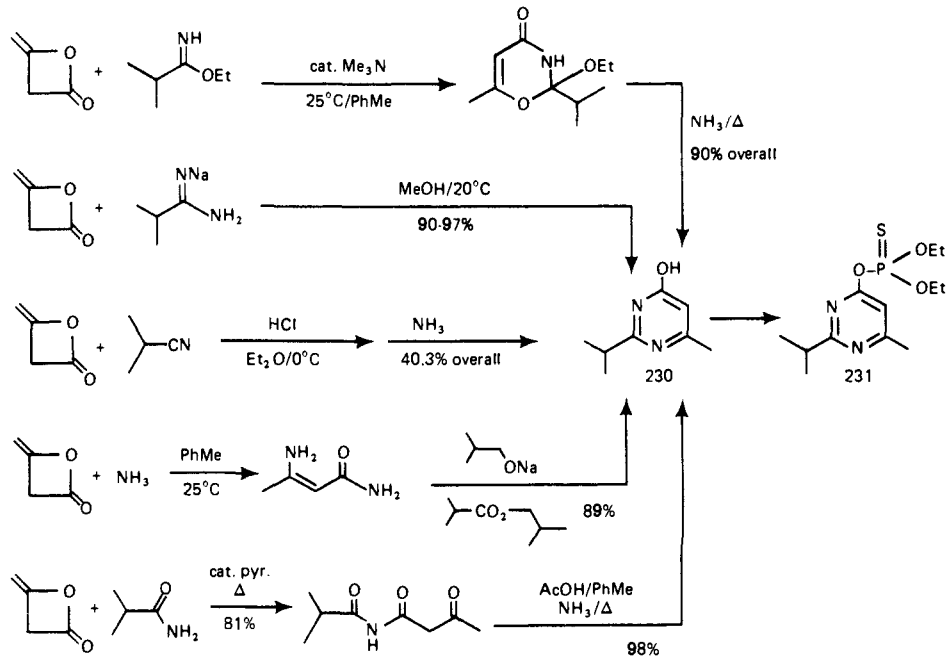
Diketene generally reacts with 2-aminoheterocycles to produce fused, bicyclic products. The simplest example of this type of reaction, that of diketene and aminopyridine, has been thoroughly investigated because of an erroneous (and irreproducible) report on the subject.[383] In fact, diketene reacts with 2-aminopyridine in benzene to afford a mixture of *N*-2-pyridylacetoacetamide (**279**) and pyrido[1,2-*a*]pyrimidinone **280**[384] (Scheme CXXI). Diketene combines with 2-aminopicolines in a similar manner.[384,385] In many cases, an aminopyridine is allowed to react with diketene under neutral conditions, and then an acidic catalyst is added to facilitate cyclization.[385] However, the reaction of 2-aminopyridine and diketene is exothermic and rapid; no intermediate can be isolated.

Many other aminoheterocycles have been reacted with diketene and with acetoacetate esters. Several types of products are produced in these reactions, but little systematic effort has been applied toward controlling which product is formed. In many instances, yields of the "desired" product are low, but the reagents are inexpensive and the product isolation has proven straightforward; these facts apparently discourage efforts to improve the yields.

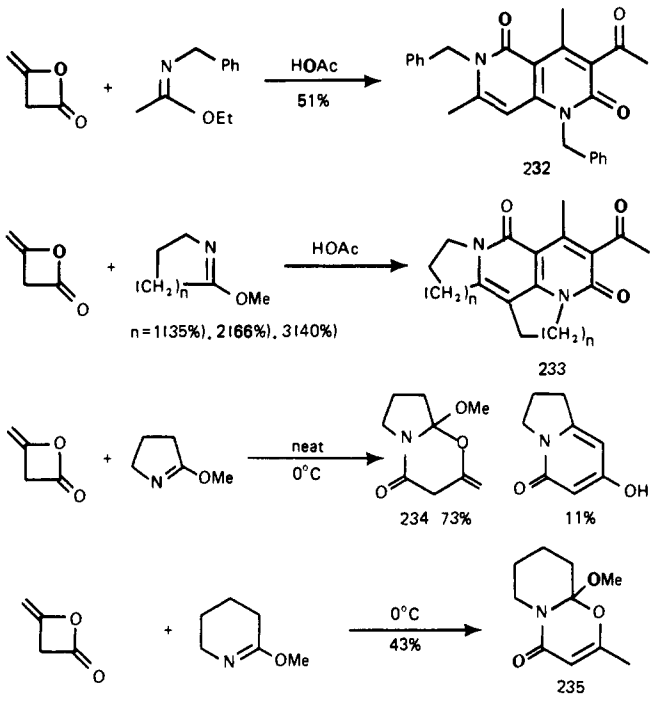
The reaction of 4-aminopyridine with diketene was originally believed to provide the pyridone **281** (R = H),[381] but this structure assignment was later revised to that of the isomeric pyrone **282**[386] (Scheme CXXII). Throughout this review, it can be seen that reactions of diketene under basic conditions frequently lead to the formation of 3-substituted 2,6-dimethyl-4-pyrones.

A series of aminopicolines and other methylated aminopyridines were treated with excess diketene to give a mixture of acetoacetamides, pyrones, and pyridones (Scheme CXXII). In general, 2-aminopicolines gave the corresponding acetoacetamide, 3-aminopicolines gave pyridones (e.g., **283**), and the more basic 4-aminopicolines provided pyrones.[386] Early reports[387] that 4-aminoquinoline, when treated with excess diketene, afforded exclusively the pyridone derivative may therefore merit reexamination. 2-Aminoquinoline furnishes the corresponding acetoacetamide in excellent yield upon reaction with diketene,[387] as do a variety of other aminoheterocycles.[381]

SCHEME CIII



SCHEME CIV



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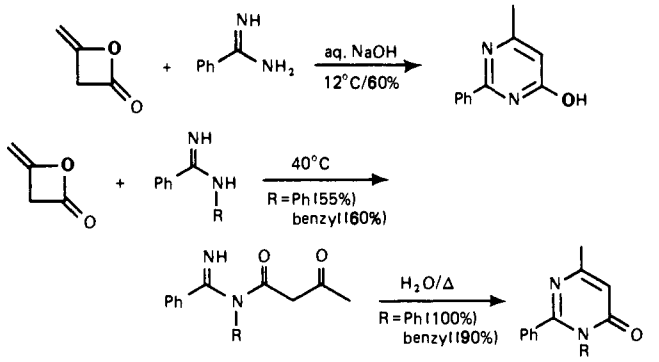


2-Amino-5-aryl-1,3,4-oxadiazoles react with diketene to afford the isomeric bicyclic systems **284** and **285**, which are claimed to be useful as bactericides and plant-growth inhibitors[388] (Scheme CXXIII).

2-Amino-1,3,4-thiadiazole reacted with excess diketene under basic conditions to afford equal amounts of the N-acetoacetylated adduct **286** and the 4-pyrone **287**[389] (Scheme CXXIV); the pure acetoacetamide **286** was more efficiently (84% yield) prepared in the absence of a basic catalyst.[390] This acetoacetamide (**286**) cyclized in concentrated sulfuric acid to afford thiadiazolo[3,2-*a*]pyrimidin-7-one[390] but was transformed into the isomeric thiadiazolopyrimidine **288** if toluenesulfonic acid was used as the catalyst.[391] The condensation of 2-amino-1,3,4-thiadiazole with ethyl acetoacetate in the presence of polyphosphoric acid afforded a low yield of **288**.[390]

2,5-Diamino-1,3,4-thiadiazole (**289**) reacted with a stoichiometric quantity of diketene in water to afford a precursor to thiazolopyrimidine **290**. With excess diketene, a bis acetoacetate (**291**) was formed and could not be cyclized[392] (Scheme CXXV).

2-Amino-1,3,4-thiadiazines, such as **292**, react with diketene to give preparatively useful yields of compounds (e.g., **293**) with antiinflammatory activity[393] (Scheme CXXVI). The interaction of 3-amino-5,6-dimethyl-1,2,4-triazine and diketene is more complex. Thus, a mixture of the triazine and 2 equiv of diketene in benzene at reflux afforded **294**, which was the result of the expected cyclization plus an acetonylation resembling the reaction of diketene with isoquinoline.[394]

Aminoisoxazolines derived from aminopentoses have been converted into nucleoside derivatives (**295**) via intermediate adduct **296**[395] (Scheme CXXVII).

2-Aminobenzoxazole was treated with diketene at 20 °C to give a hemiaminal (**297**), which could be dehydrated to provide a single product (**298**) (Scheme CXXVIII); two tricyclic isomers were observed when the reaction was run in refluxing benzene.[396] Benzindoline-2-thione (**299**) and benzimidazol-2-thione react with diketene to provide fused heterocyclic products via a similar N-acetoacetylation.[397]

The hemiaminals (**300**) which precipitated from the reaction of diketene with 2-anilino-2-imidazolines at −5 °C showed analgesic activity; these hemiaminals (**300**) are easily dehydrated[398] (Scheme CXXIX).

2-Aminothiazoline **301** and 2-aminothiazine **302** reacted with diketene to afford bicyclic systems **303** and **304**; the latter compound (**304**) is converted into a β-lactam (**305**) upon photolysis[399] (Scheme CXXX).

Some aminoheterocycles have been functionalized on the free amino group prior to reaction with diketene, often via imine or imidate formation. These functionalized heterocycles undergo ring closure via the active methylene group of an acetoacetylated intermediate.[400] For example, the formimidate of 2-aminopyridine (**306**) reacts with diketene to afford pyridopyrimidone **307**[401] (Scheme CXXXI).

Another example of N-acetoacetylation followed by ring closure is the reaction of diketene and benzimidoacetate **308** to give the fused, tricyclic ring system **309** in excellent yield[374] (Scheme CXXXII). A more extensively functionalized analogue (**310**) of this benzimidoacetate also reacted with diketene to afford a fused, tricyclic heterocycle. The analogous benzothiazole reacted similarly, while the benzoxazole failed to react.[402]

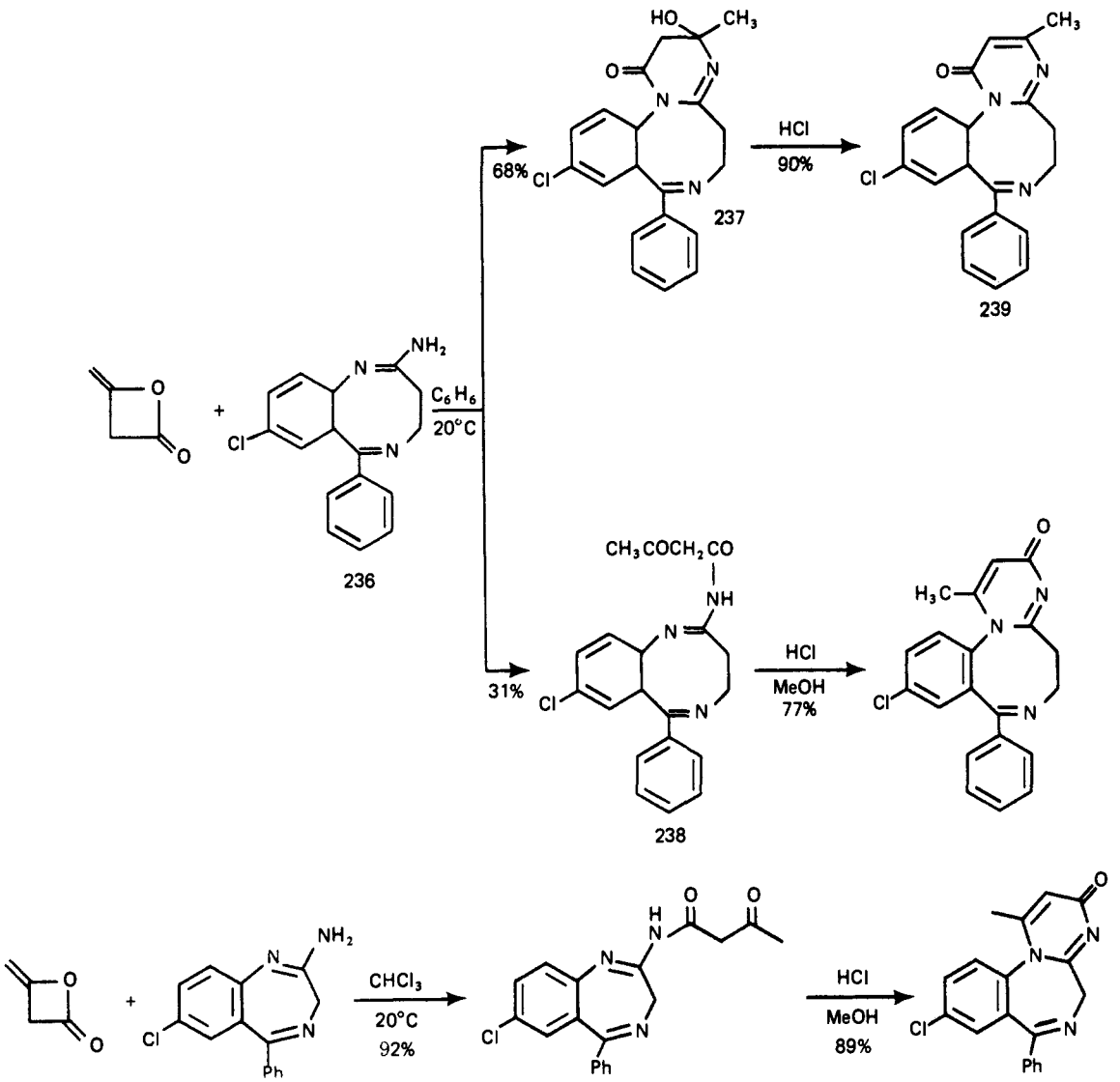
Also, 2-pyridyl isocyanate and isothiocyanate react with diketene to yield pyridopyrimidones **311**[403] (Scheme CXXXIII).

G. Reactions with Ureas

It has long been known that diketene reacts with urea to give 6-methyluracil (**312**)[404] (Scheme CXXXIV). While this reaction proceeds in the absence of a catalyst (toluene, reflux),[405] the yield can be greatly improved with a catalyst such as pyridine[406] or a mercury(II) salt.[407] Recent improvements in the preparation of 6-methyluracil from diketene include the use of diazabicyclo[2.2.2]octane (DABCO) as a catalyst in $AcOH/Ac_2O$ solvent.[408] A statistical optimization of the preparation of 6-methyluracil in a pyridine/Ac_2O/AcOH system resulted in yields of nearly 90%.[409]

In pyridine at 20 °C, diketene acetoacetylates *N*-alkylureas almost exclusively on the unsubstituted amino group, and the resulting acetoacetimides can be cyclized to give 1-alkyl-6-methyluracils (**313**) (Scheme CXXXV). The use of hot acetic acid for this latter reaction, however, affords a mixture of 1- and 3-alkyluracils.[410] The

SCHEME CVI



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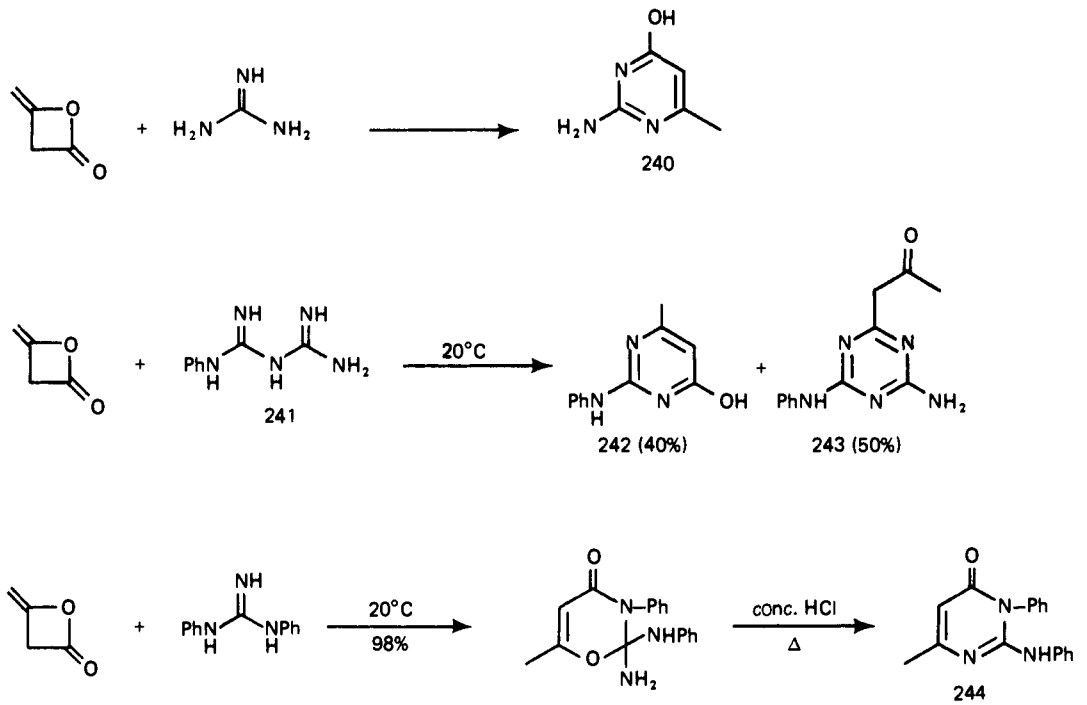
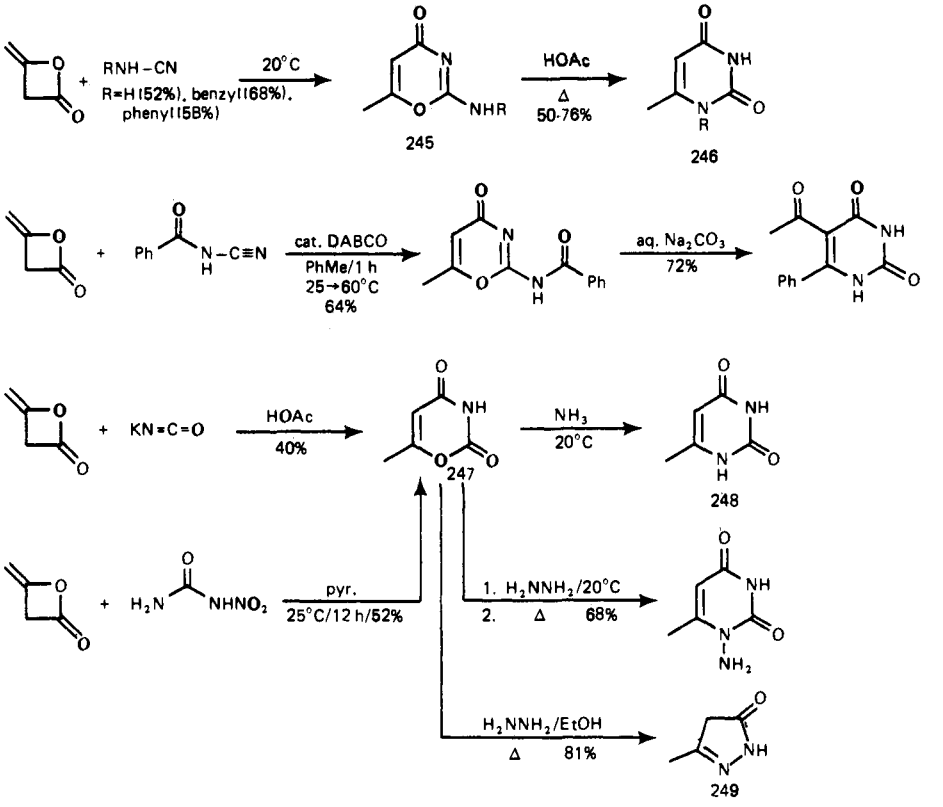
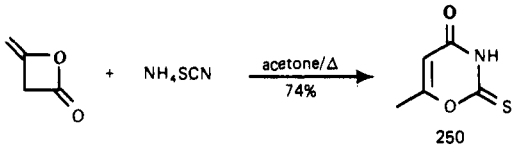


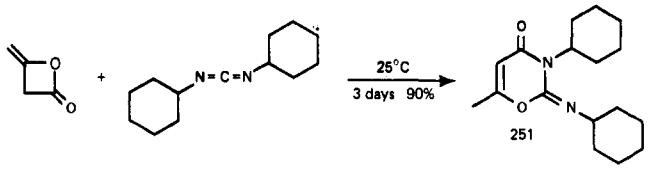
SCHEME CVIII



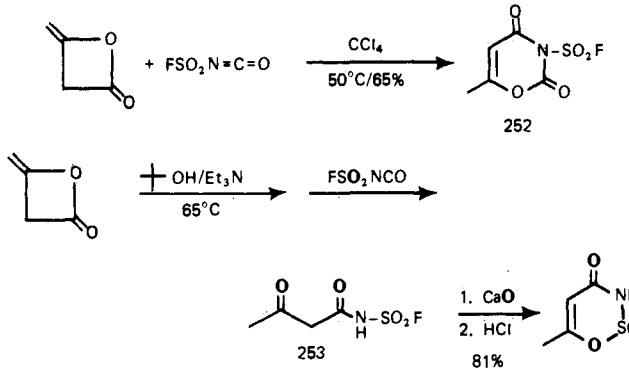
SCHEME CIX



SCHEME CX



SCHEME CXI



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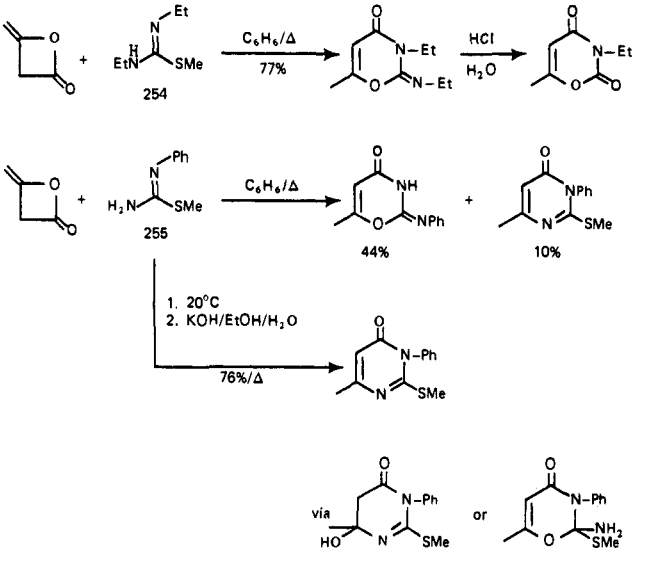


reaction of *N*-phenylurea with diketene appears to be more complex and gave both 6-methyl-1-phenyluracil (**314**) and the 4-pyrone **315** from the same reaction mixture.[411]

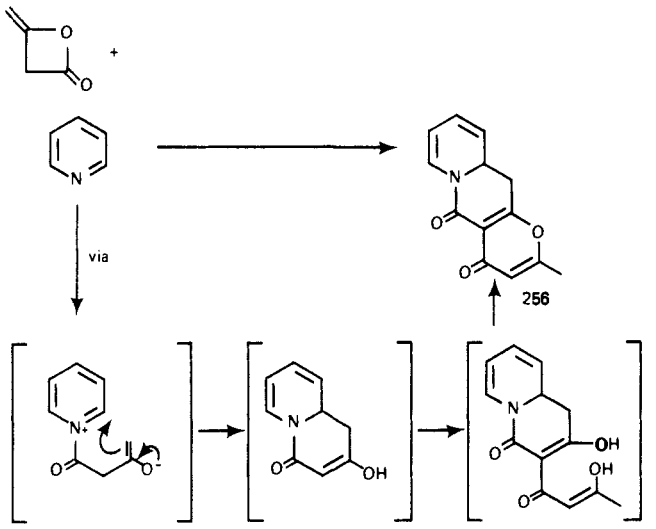
Authentic samples of 1-substituted and 3-substituted 6-methyluracils have been prepared from diketene by other routes[410,412] (Scheme CXXXVI); one 3-substituted uracil (**316**) is a preemergent herbicide.[413] Two closely related analogues of **316**, terbacil (**317**) and bromacil (**318**), are also herbicides.

N,N-Dimethylurea reacts with diketene in acetic acid at 90 °C to afford 6-methyl-1,3-oxazin-2,4-dione (**247**) in over 60% yield (Scheme CXXXVII); this oxazine is easily converted into uracils.[414]

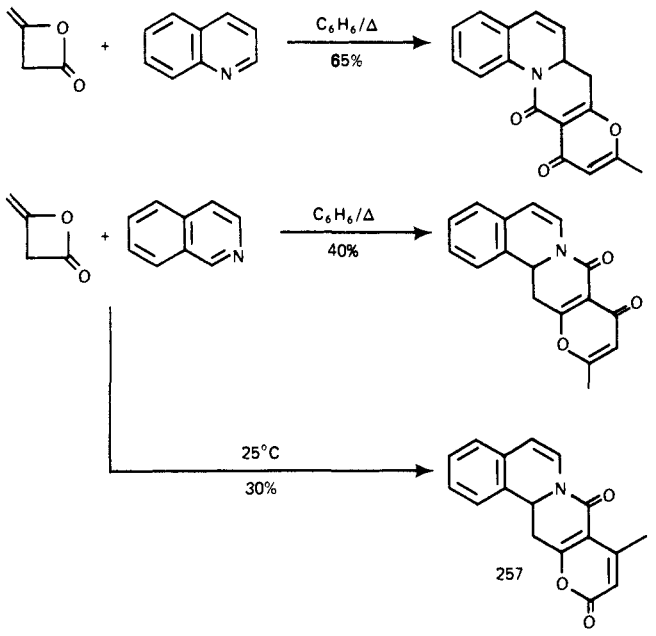
N,N′-Disubstituted ureas react with diketene to give low to moderate yields of the corresponding uracils (**320**) (Scheme CXXXVIII), some of which exhibit analgesic and antiinflammatory activity.[415]

Diketene and thiourea combine under basic conditions to form a 4-pyrone (**321**)[411] but give the thiouracil **322** under acidic conditions[359] (Scheme CXXXIX).

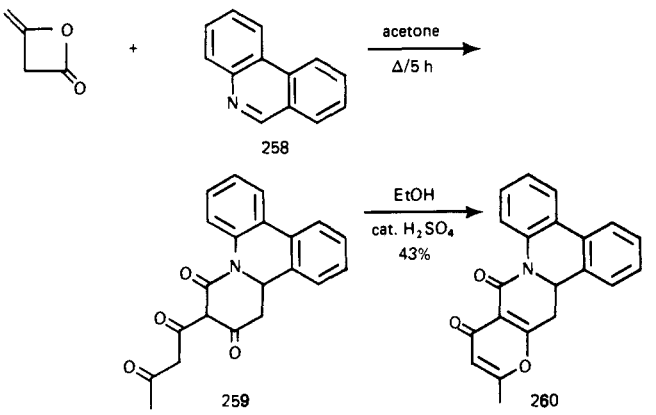
SCHEME CXIII



SCHEME CXIV



SCHEME CXV

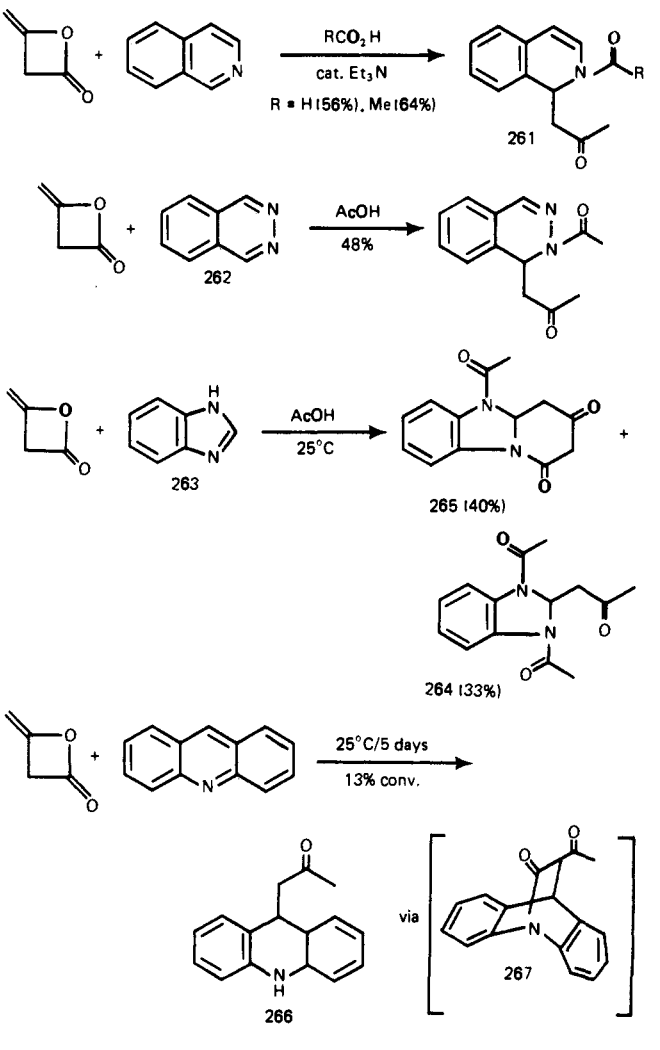


The 1,3-diphenyl-2-thiouracil analogous to compound **320** has been prepared from diketene and *N,N'*-diphenylthiourea.[397]

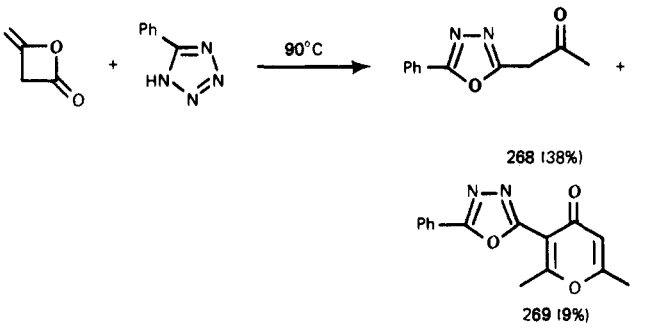
Under basic conditions, sulfamide and diketene react to provide the 2,1,3-thiadiazine derivative **323**,[416] which is readily brominated to afford a product (**324**) that acts as a bromonium ion source[417] (Scheme CXL). Thus, the bromine in **324** can be quantitatively titrated with iodine, while the bromine in the analogous 5-bromouracil is essentially unaffected by iodine.

N-alkylsulfamides and diketene combine to afford either 1- or 3-substituted 2,1,3-thiadiazine *S,S*-dioxides, depending upon the reaction conditions used[417,418] (Scheme CXLI). Basic reaction conditions result in the formation of 1-substituted 2,1,3-thiadiazines (**325**), while acidic conditions give the 3-isomer (**326**).[418] However, in an attempt to prepare glycoside analogues of **325**, diketene was reacted with *N*-(tetrakis-*O*-acetylglucopyranosyl)sulfamide in nitromethane at 20

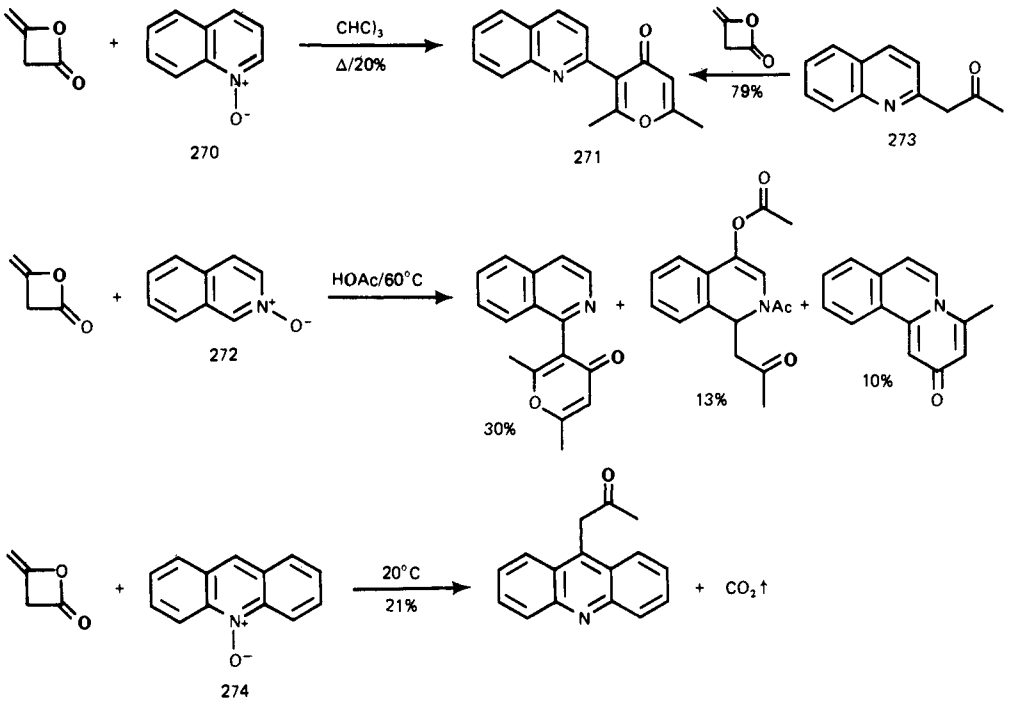
SCHEME CXVI



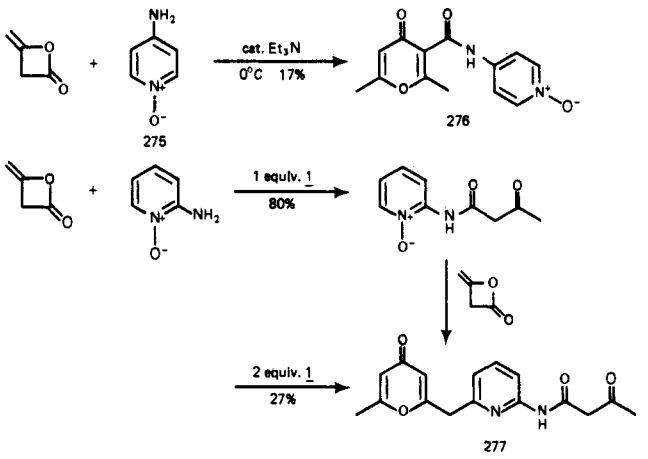
SCHEME CXVII



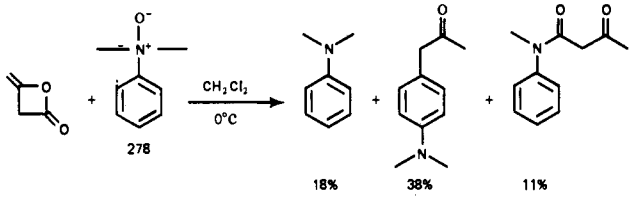
SCHEME CXVIII



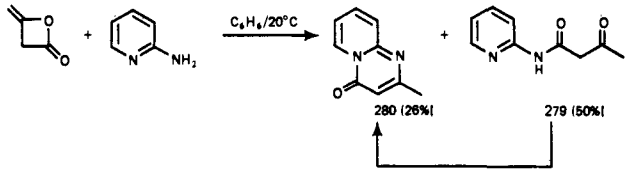
SCHEME CXIX



SCHEME CXX



SCHEME CXXI



°C with pyridine as a catalyst; pyrone formation resulted. These reaction conditions favored pyrone formation even in the absence of the glycoside,[419] a result which is consistent with other pyridine-catalyzed diketene reactions throughout this review (c.f. compounds **315**, **321**).

Treatment of phosphonamides with diketene provides phosphadiazines (**327**)[420] (Scheme CXLII), which can undergo a variety of further reactions.[421]

The reaction of diketene with semicarbazones resembles that of diketene and urea, and yields *N*-imino uracils (**328**)[422] (Scheme CXLIII). An isomeric 3-aminouracil is obtained from the reaction of acetone thiosemicarbazone and diketene.[423] If the free amino group of a semicarbazone were to be hindered or deactivated, then the imine would be expected to react with diketene (see section IV.D).

H. Acid-Catalyzed Cyclization of Acetoacetates and Acetoacetarylides

Phenyl acetoacetates prepared from diketene can be converted into coumarins (**329**) by acid-catalyzed cyclization (Scheme CXLIV). As would be expected, the cyclization reaction becomes more facile with the addition of electron-donating substituents on the aromatic rings. Thus, while *p*-chlorophenyl acetoacetate provides only 1% of the corresponding coumarin, resorcinol monoacetoacetate cyclizes rapidly and in excellent yield.[424]

Aryl acetoacetates can be prepared from phenols and diketene in the presence of a base or in the presence of a catalytic amount of acid at low temperature. Coumarins become the expected reaction product when an excess of concentrated strong acid is used as the reaction solvent.[425]

The reactions of dihydroxynaphthalenes with diketene and the subsequent cyclization of the resulting acetoacetates have been extensively studied. Some of these dihydroxynaphthalene acetoacetates cyclize at room temperature[426] (Scheme CXLV).

4-Substituted aryl acetoacetates (e.g., **330**) have been converted into coumarins such as **331** in good yield; the

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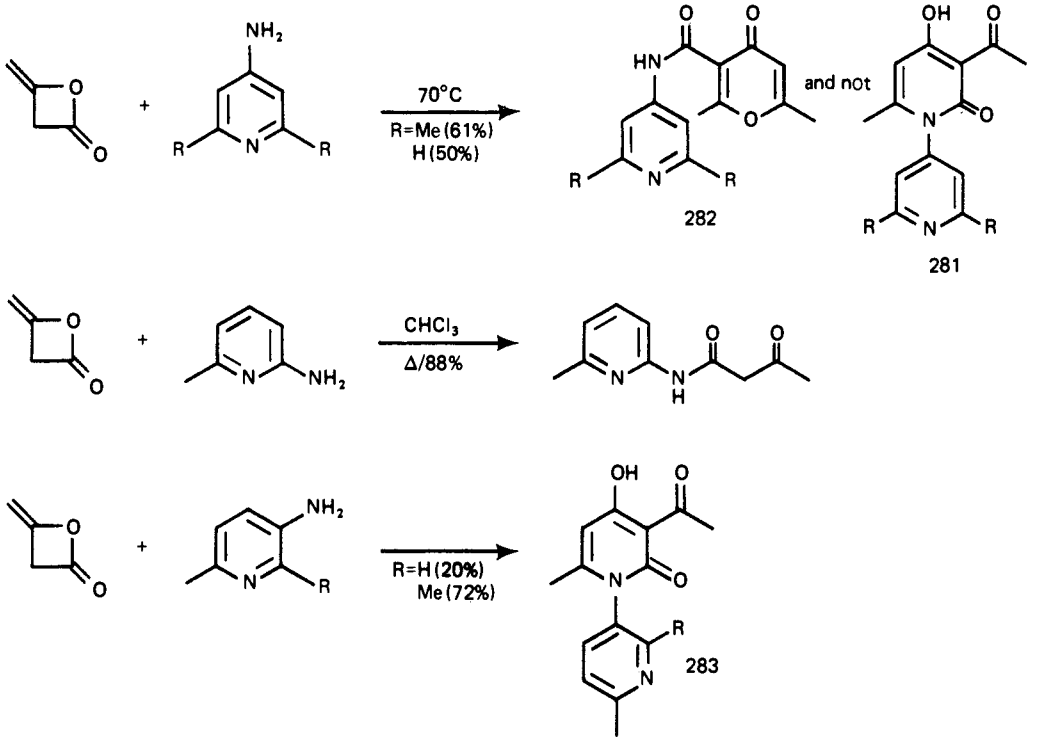
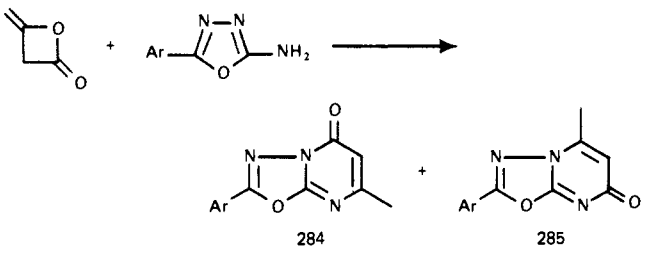


SCHEME CXXIII



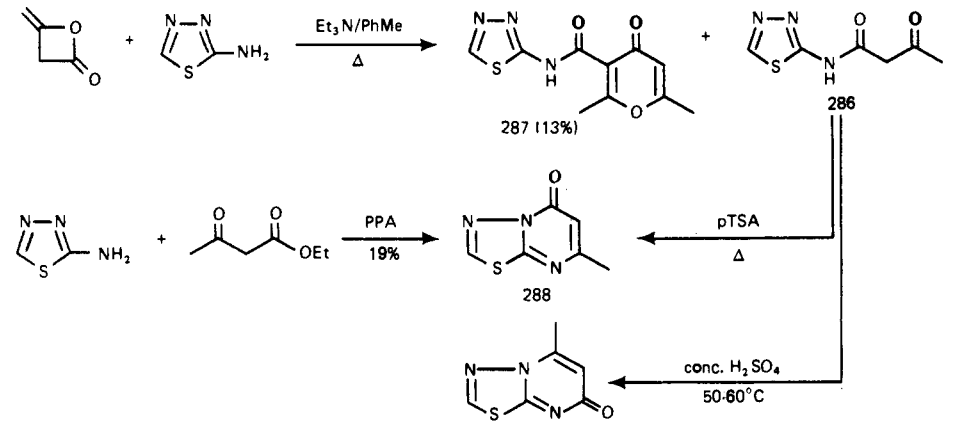
halogen facilitates further elaboration of these coumarins[427] (Scheme CXLVI).

Aromatic thiols have been acetoacetylated and cyclized with polyphosphoric acid (PPA). This reaction results in the formation of either a thiocoumarin (**332**) or a thiochromone (**333**), depending the specific thiophenol used (Scheme CXLVII). The literature regarding this cyclization is complicated by the fact that many workers had prepared their starting materials via the acid-catalyzed reaction of thiols and diketene and were therefore working with 3-arylthiocrotonic acids instead of aryl acetothioacetate esters.[198] It appears that chromone formation is generally favored from either of these precursors, although 3-methoxybenzenethiol provides the coumarin in both instances.[428] Likewise, a selenochromone has been prepared from diketene and selenophenol, but the structure of the intermediate is unclear.[204] A definitive study of the preparation and structure of thio- and selenocoumarins and thio- and selenochromones from diketene would be most helpful.

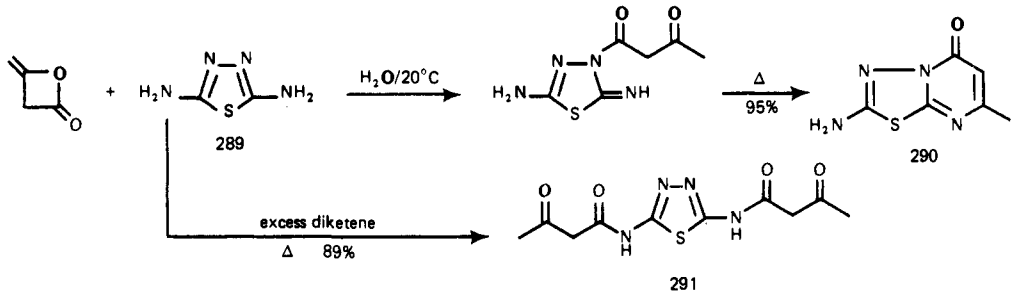
Acetoacetarylides cyclize to afford quinolone derivatives, and some vasodilators (**334**)[429] and cyan dye couplers[430] have been prepared by such cyclization (Scheme CXLVIII). An acid-catalyzed cyclization of an acetoacetarylide has been used in the total synthesis of the alkaloid eupolauramine (**335**).[431]

In the case of *m*-phenylenediamine, treatment with 1 mol of diketene results in rapid cyclization to the aminoquinolone **336**, but the second equivalent results only in acetoacetylation[432] (Scheme CXLIX). A similar

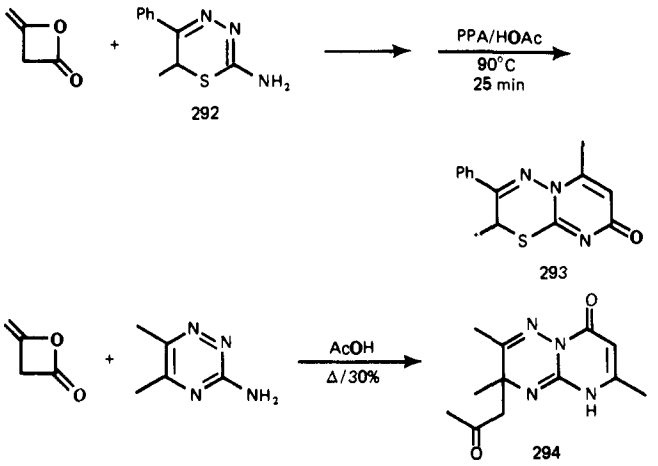
SCHEME CXXIV



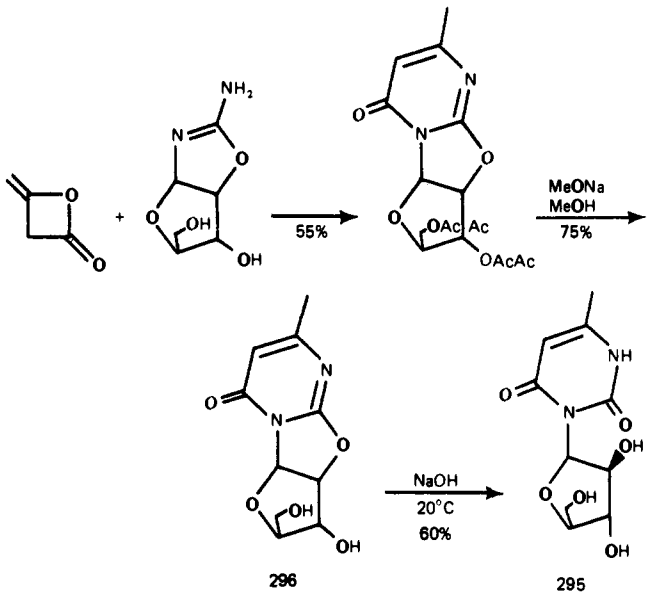
SCHEME CXXV



SCHEME CXXVI



SCHEME CXXVII



failure to effect a bis cyclization was encountered during the synthesis of nybomycin (**337**);[433] note the regiochemistry of the second cyclization.

A compound (**338**) with antihypertensive activity has been prepared via acid-catalyzed cyclization of an acetoacetylated tetrahydroquinoline derivative[434] (Scheme CL).

The hydroxyquinolizinone **339** reacts with diketene in acetic acid to give a fused heterocycle[435] (Scheme CLI).

A series of indoles and indolines has been acetoacetylated and then cyclized into fused heterocycles with PPA[436] (Scheme CLII).

I. Miscellaneous Preparations of Six-Membered Rings

There is a series of diketene reactions in which a heteroatom is acetoacetylated and then the methylene group of the resulting acetoacetate is condensed with an electrophilic carbon atom. For example, salicylaldehyde is acetoacetylated and the resulting adduct undergoes a Knoevenagel condensation to afford 3-acetylcoumarin (**340**)[437] (Scheme CLIII).

7-Acetyl-6-aminotetralin (**341**) reacts with diketene by an acetoacetylation/ring-closure sequence to give the cyclohexaquinolone derivative **342**[438] (Scheme CLIV). 2,4-Dihydroxyquinoline **343** can be prepared from methyl anthranilate and diketene.[439] The N-acetoacetylation of carboline **344**, followed by base-catalyzed cyclization, provided the D ring of geissoschizine (**345**).[440]

Aminoacetylpyrroles such as **346**, and N-1-functionalized analogues thereof, have been acetoacetylated with diketene and then cyclized with base to afford bicyclic systems (**349**) (Scheme CLV), which inhibit the activity of prostaglandin synthetase.[441] A series of red-violet anthraquinone dyes (e.g., **350**) has been prepared by acetoacetylation/ring-closure reactions with diketene.[442]

Several β-hydroxy ketones react with diketene to give acetoacetates which provide lactones after ring closure. For example, diacetone alcohol can be acetoacetylated and then treated with potassium hydroxide to afford dihydropyrone **351**[443] (Scheme CLVI); other β-hydroxy aldehydes react similarly. This cyclization of hydroxy ketones is more general and therefore more commonly used for the preparation of five-membered rings from α-hydroxy ketones (see section V.C).

The condensation of the active methylene group of an acetoacetarylide onto a nitro group provides a novel route to quinoxalone *N*-oxides such as **352**[444] (Scheme CLVII).

Diketene reacts with *o*-aminobenzamide to afford a dyestuff precursor (**353**)[445] (Scheme CLVIII). The related benzoxazinone **354** is prepared from the reaction of diketene and anthranilic acid. Adduct **354** can be treated with methylhydrazine to provide an aminopyrazole which is readily converted into a series of compounds (e.g., **355**) that are useful as viruscides and antidepressants.[446]

V. Five-Membered Heterocycles Derived from Diketene

A. Reactions with Hydrazines

The reaction of hydrazines with acetoacetate esters is commonly used to prepare pyrazolones, but these

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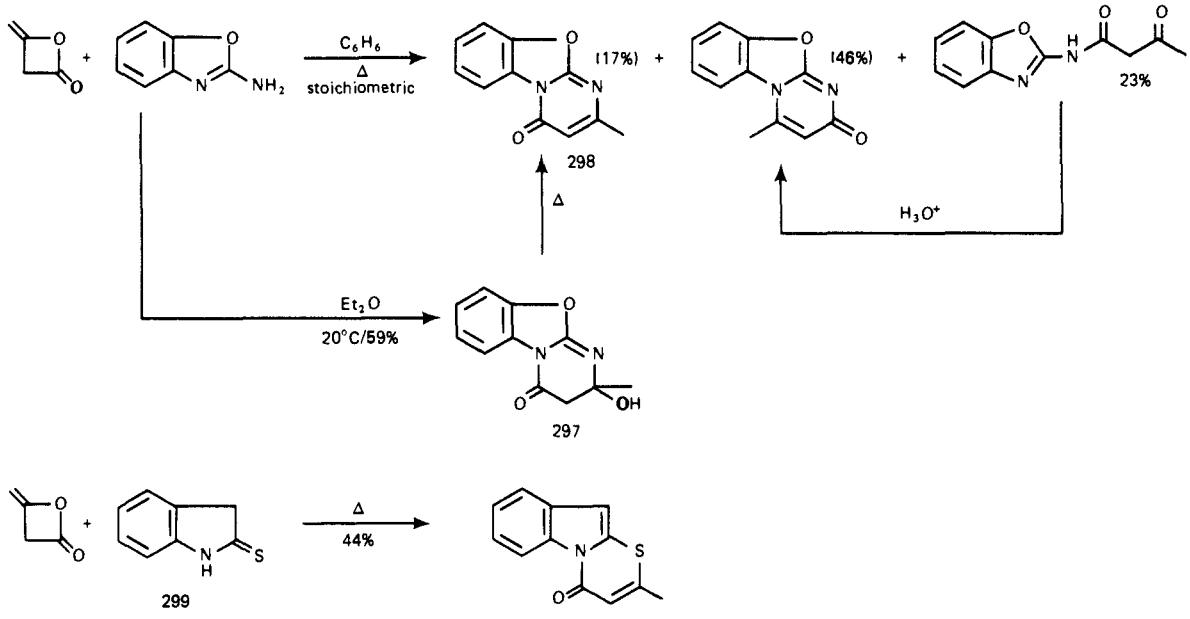
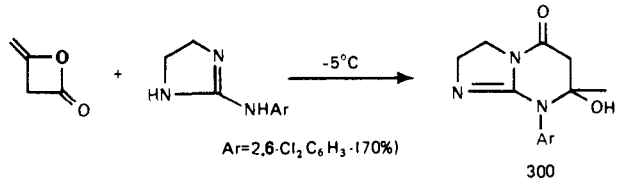


SCHEME CXXIX



pyrazolones can also be prepared directly from hydrazines and diketene. Thus, hydrazine hydrate is claimed to react with diketene in methanol to afford an excellent yield of 5-methyl-3-pyrazolone (**356**)[447] (Scheme CLIX). Pyrazolone **356** has also been prepared in low yield from diketene and acetyl hydrazide.[448] Methylhydrazine and diketene react to provide 2,5-dimethyl-3-pyrazolone (**357**) in excellent yield; other alkyl pyrazolones were similarly prepared.[449]

5-Methyl-3-pyrazolone is readily alkylated on the active methylene group and couples with diazo compounds to form intermediates of great importance in dyestuff manufacture. Also, the hydrazine moiety in 3-pyrazolones can be exchanged with substituted hydrazines to prepare substituted pyrazolones.[450]

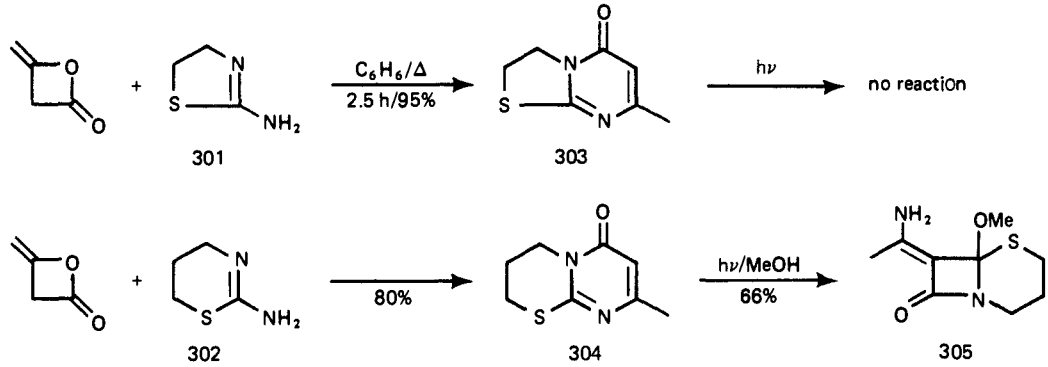
Phenylhydrazine reacts with diketene to give *N'*-phenylacetoacetohydrazide 3-phenylhydrazone (**358**),[9] which provides a 2-phenyl-3-pyrazolone (**359**) upon heating with an additional equivalent of diketene (Scheme CLX). Presumably this additional diketene rapidly removes phenylhydrazine from the equilibrium because, if this ring closure is effected in hydrochloric acid without the addition of diketene, the isolated product is 1-phenyl-3-pyrazolone **360**.[451] Therefore, it is possible to selectively prepare either of the two 3-pyrazolone isomers from a common intermediate. A mild, one-pot reaction is used to prepare commercially desirable 5-methyl-2-aryl-3-pyrazolones such as **361**.[452] These arylpyrazolones are coupled with diazonium salts to form colorants, such as the pyrazolone pigment **362**, which is known as Pigment Yellow 10.

Phenylhydrazones of aromatic ketones and aldehydes react with diketene (acetic acid, reflux) to give pyrazolin-3-ones (**363**) (Scheme CLXI). Phenylhydrazones of most aliphatic carbonyl compounds provide similar products (**364**) when heated with diketene in benzene that contains a trace of acid.[453] Cyclic hydrazones (pyrazolines) react with diketene under neutral conditions to afford fused piperidine-2,4-diones (**365**).[454]

A pyridazin-3-one derivative (**366**) with antihypertensive activity has been prepared from diketene and benzil monohydrazone[455] (Scheme CLXII).

Other types of molecules with N–N bonds also react with diketene. Hydrazobenzene and diketene combine, in the presence of triethylamine, to give a good yield

SCHEME CXXX



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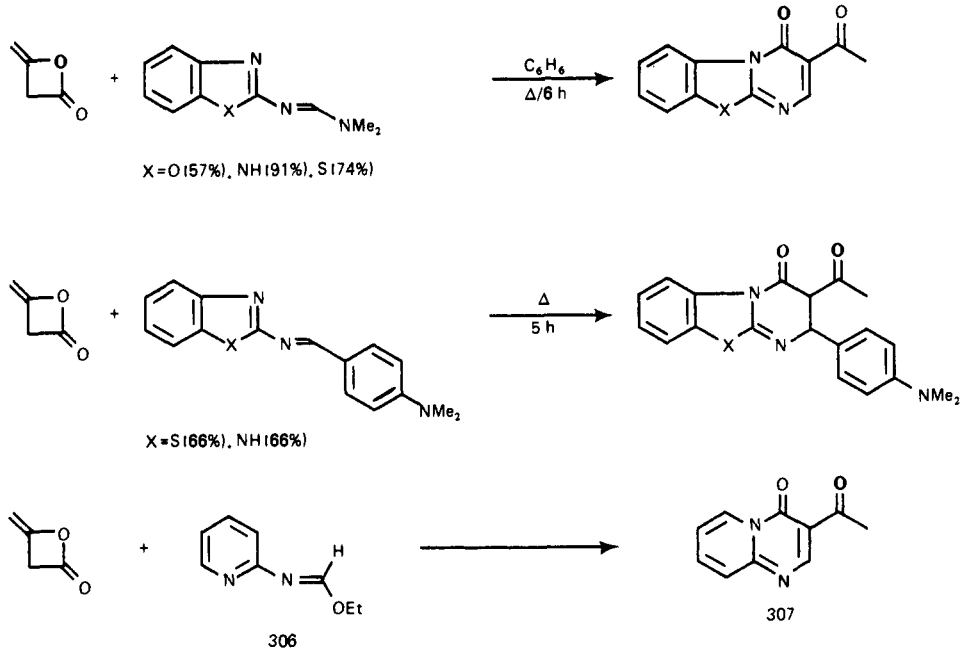

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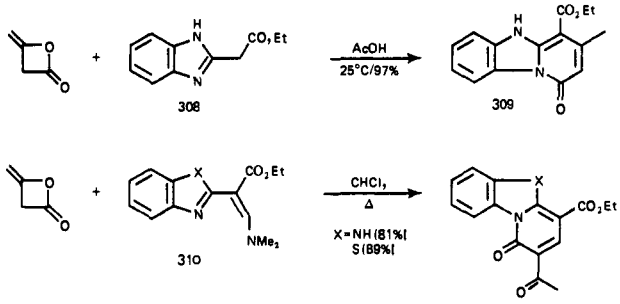

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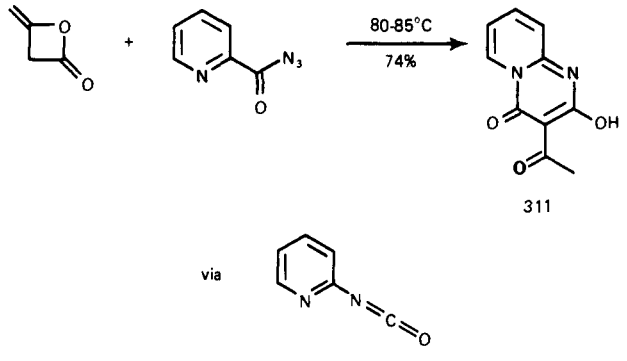
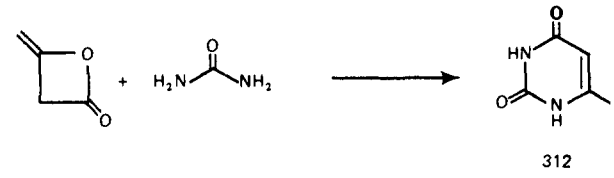


of 3-pyrazolone **367**[456] (Scheme CLXIII). The photolytic reaction between an azo compound and diketene results in the formation of a piperidazinedione (**368**). In this latter example, the preparation of a large number of analogues demonstrated that only one isomer is obtained from unsymmetrical azo compounds.[457]

Diketene reacts with 1-(ethylamino)-3-methylindole (**369**) to provide the tricyclic ring system **370**[458] and also with 1-iminopyridinium (**371**) and 1-iminoquinolinium ylides to provide bicyclic ring systems such as **372**[459] (Scheme CLXIV). The acetoacetylated ylide **373** was an isolable intermediate and required a strong base for cyclization.

Unexpectedly, treatment of *N*-phenyl-*N*-methyl-

SCHEME CXXXIV



hydrazine with diketene and then with PPA afforded the fused heterocycle **374** (Scheme CLXV). One intermediate (**375**) was isolated.[460]

B. Reactions with Hydroxylamine and Derivatives

Under most conditions, diketene or acetoacetate esters react with hydroxylamine to give 3-methylisoxazol-5-one (**376**)[461,462] (Scheme CLXVI). It has recently been shown, however, that the isomeric 3-hydroxy-5-methylisoxazole (**377**) can be prepared from diketene and hydroxylamine by carefully maintaining the pH between 9 and 10; in this pH range the free hydroxylamine is the predominant species and will thus be acetoacetylated on nitrogen.[463]

The 3-hydroxy-5-methylisoxazole (**377**) is a useful plant protecting agent, known as Tachigaren or Hymexazol, and a variety of synthetic routes to this compound have been developed. Thus, *N*-acetoacetyl-*O*-benzylhydroxylamine (**378**) was produced with a stoichiometric amount of diketene in the absence of a catalyst (Scheme CLXVII). Debenzylation of **378**, followed by treatment with acid, afforded 3-hydroxy-5-methylisoxazole (**377**).[462] The preparation of this agrichemical has been refined by the incorporation of an acid-labile blocking group on the oxygen, such as the *tert*-butyl group. An attempted use of an *O*-acyl protecting group resulted in Lossen rearrangement of the intermediate acetoacetamide and, consequently, in the preparation of oxazol-2-one **379** in good yield.[464]

N,*O*-Bis(trimethylsilyl)hydroxylamine (**380**) was treated with diketene and the resulting acetoacetate was

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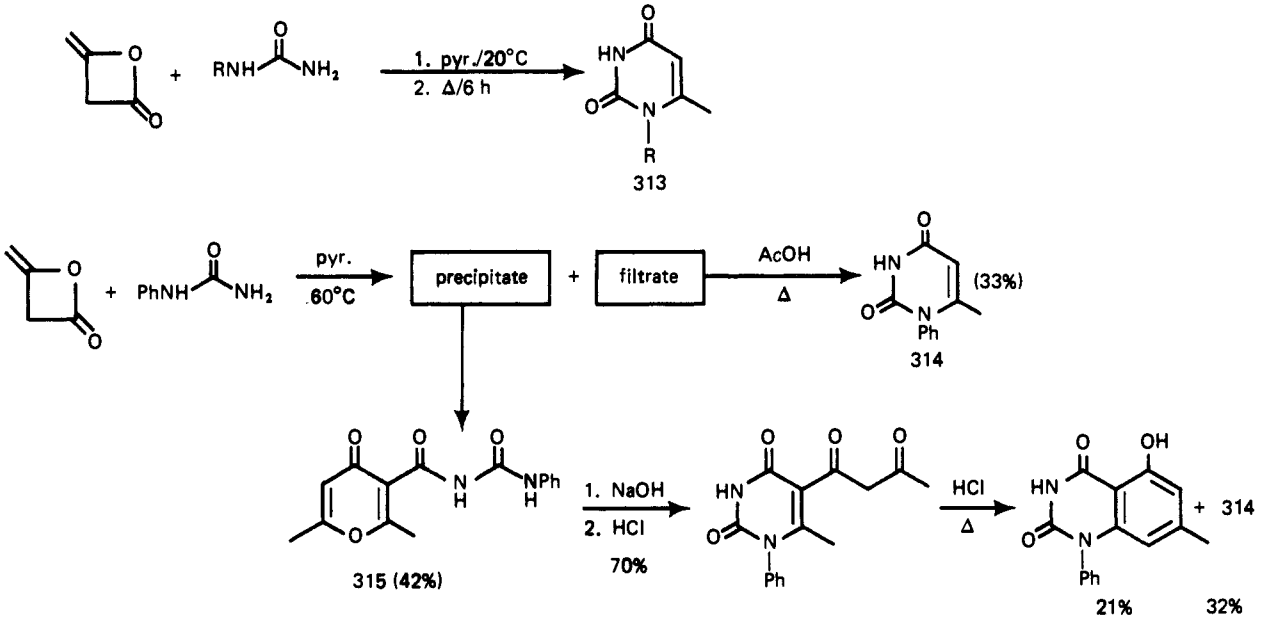
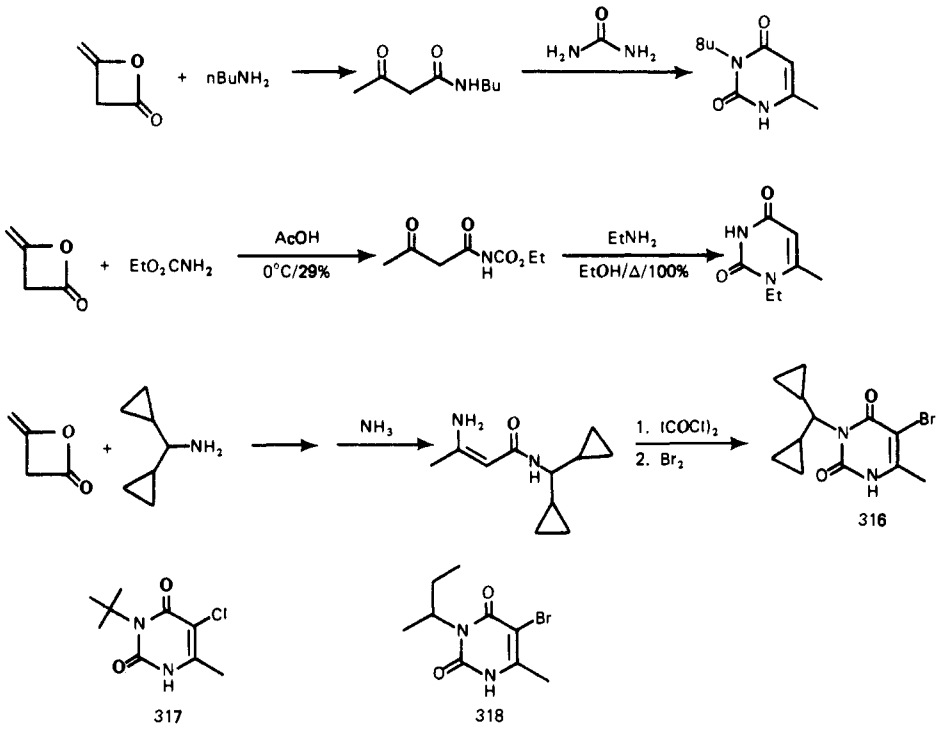
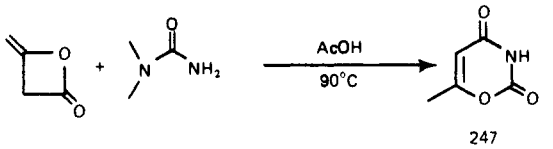


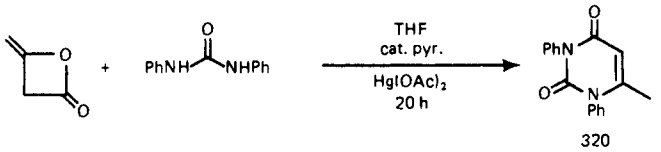
SCHEME CXXXVI



SCHEME CXXXVII



SCHEME CXXXVIII

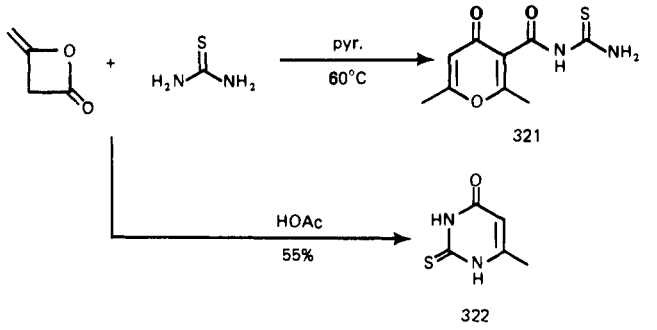


cyclized with acid to provide 3-hydroxy-5-methylisoxazole (377) (Scheme CLXVIII). This isoxazole was further elaborated into muscinol (382), a hallucinogen found in mushrooms.[465]

N-Substituted hydroxylamines are acetoacetylated on nitrogen with diketene and then rapidly cyclize to form tertiary alcohols (383) which can be either dehydrated or alkylated[466] (Scheme CLXIX).

N-Phenylacetoacetohydroxamic acid (110), readily prepared from *N*-phenylhydroxylamine and diketene, is readily cyclized in the presence of BF_3 to afford the oxazole 384[186] (Scheme CLXX). Treatment of 110 with aroyl chlorides is claimed to result in cyclization and acylation, providing a one-pot preparation of the her-

SCHEME CXXXIX



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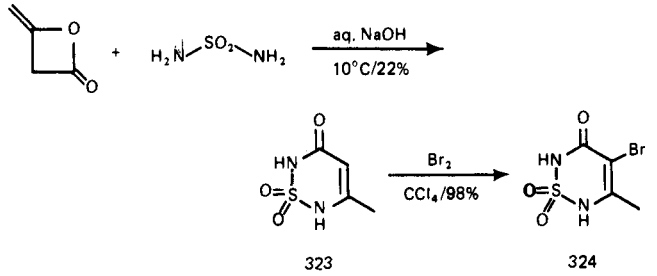


bicide **385**.[467] *N*-Hydroxylsulfonamides react with diketene to provide 3-methyl-2-sulfonylisoxazolones.[461]

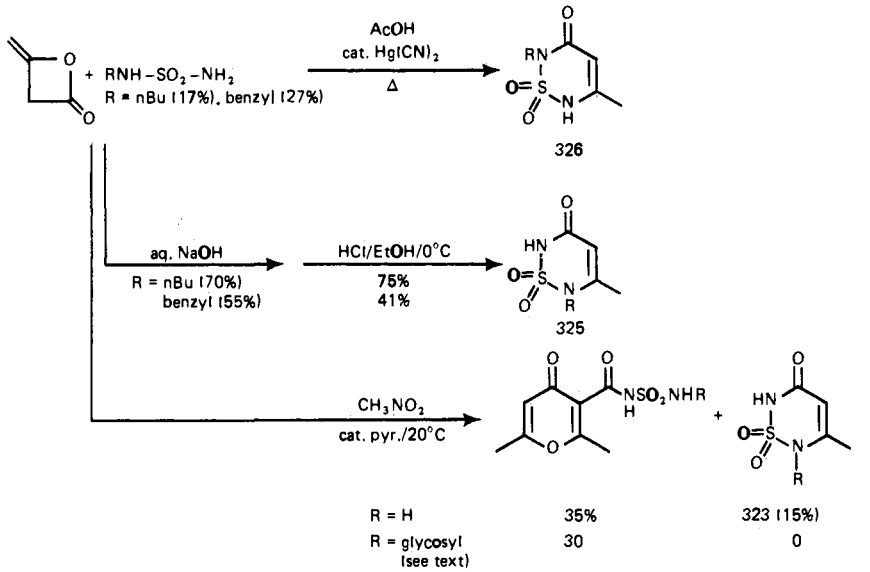
Hydroxylamine or O-substituted hydroxylamines react with excess diketene in the presence of triethylamine to provide 2-pyridones (**386**)[462] (Scheme CLXXI).

An N,O-dialkylated hydroxylamine (**387**) was treated with diketene and then with base. This reaction provided the requisite *N*-hydroxypyridone for a total synthesis of (±)-tenellin (**388**), a naturally occurring yellow pigment[468] (Scheme CLXXII).

Aliphatic amidoximes (**389**) react with diketene to afford acetonylated 1,2,4-oxadiazoles (**390**) in reasonable yields (Scheme CLXXIII); the chemistry of the acetonyl side chain has been studied.[469] The reactions of aryl-1,2,4-oxadiazoles (**391**), which are prepared from aromatic amidoxime acetoacetates **392**, have also been studied. The action of a strong base on **392** results in an alternate mode of cyclization and provides 1,2,4-oxadiazol-5-one **393**.[470]

Heterocycles containing N–O bonds have also been prepared from acetoacetate derivatives, such as the

SCHEME CXLI



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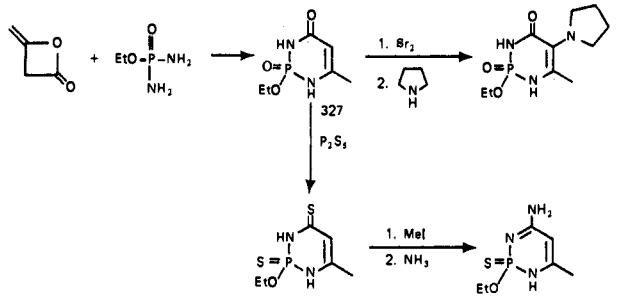
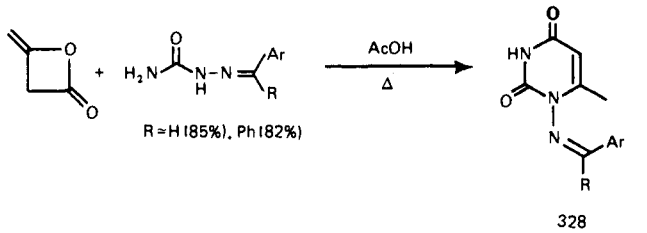


SCHEME CXLIII



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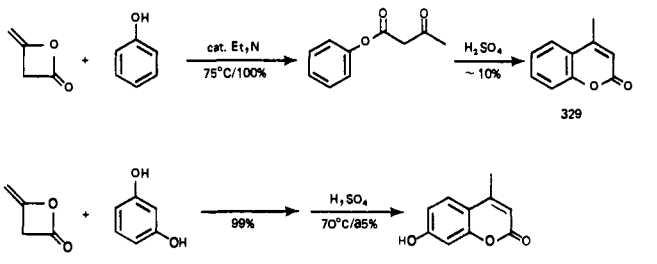

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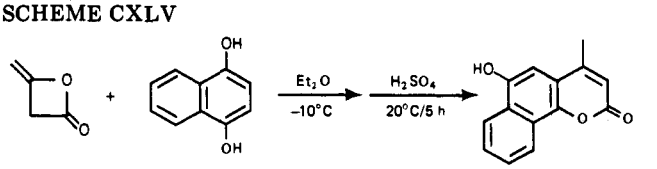

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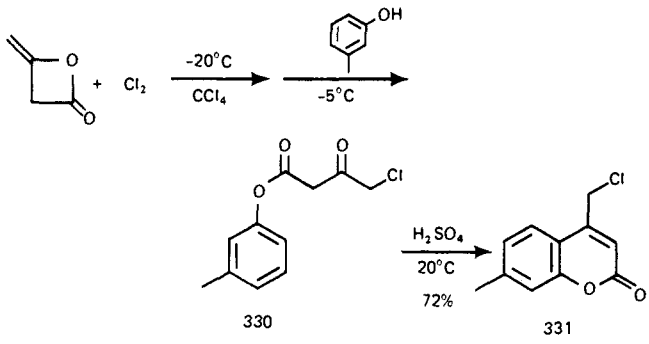


analgesic **394** prepared from an acetoacetarylide[471] (Scheme CLXXIV). A furazan (**395**) with antihypertensive activity has been prepared from an acetoacetamide.[472] The condensation of an *N*-methoxyacetoacetamide with an α-acetoxy aldehyde was used to prepare the 2,5-dimethylfuran derivative **396**[473] (Scheme CLXXV).

C. Reactions with Hydroxy Ketones

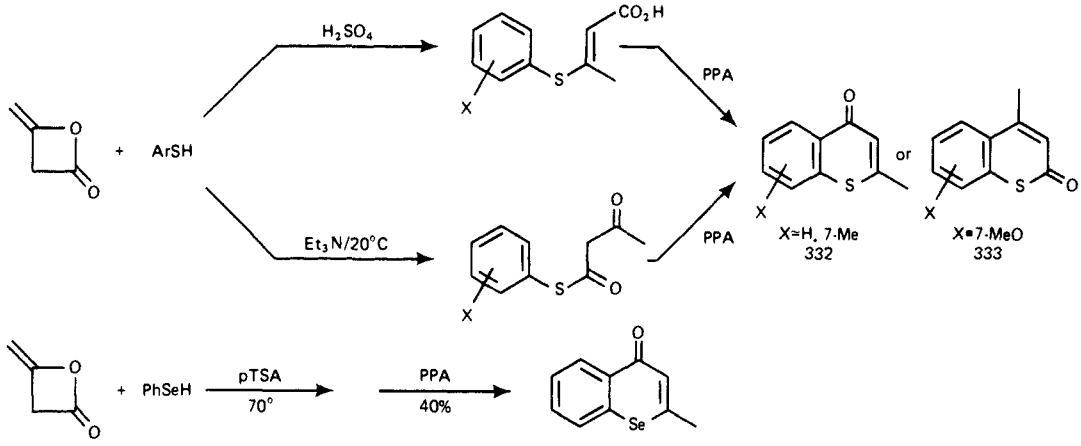
α-Hydroxy ketones undergo a sequential acetoacetylation/condensation reaction to give five-membered rings, such as the butenolide **397**, which was derived from 5-hydroxy-4-octanone[474] (Scheme CLXXVI). These butenolides are easily converted into furan-3-carboxylic acids (e.g., **398**).[474a]

Furanones such as **399** have been similarly prepared from α-hydroxy acids,[475] and *S*-carlosic acid (**400**) has been synthesized from dimethyl (*S*)-malate and diketene[476] (Scheme CLXXVII). An alternate, diketene-based approach to carlosic acid proceeds via transesterification of functionalized *tert*-butyl acetothioacetates.[477]

D. Reactions with Amino Ketones

Diketene also reacts with α-amino ketones in an acetoacetylation/condensation sequence to give pyrrolidinones, such as **401** and **402**,[478] and with α-amino acids and their esters[309b,439] to afford pyrrolidinediones **403**[479] (Scheme CLXXVIII). A number of these compounds have interesting biological properties as plant regulators,[480] depressants,[481] and antibiotics.[482,479c]

SCHEME CXLVII



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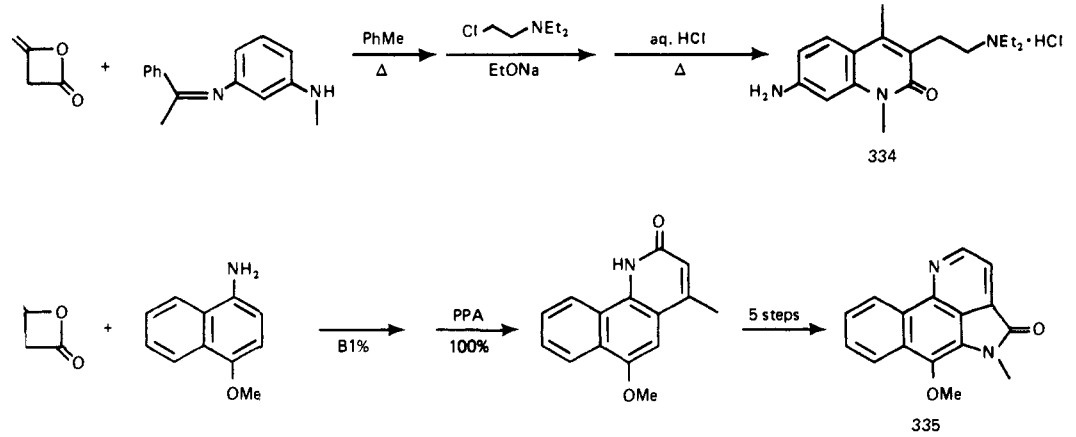

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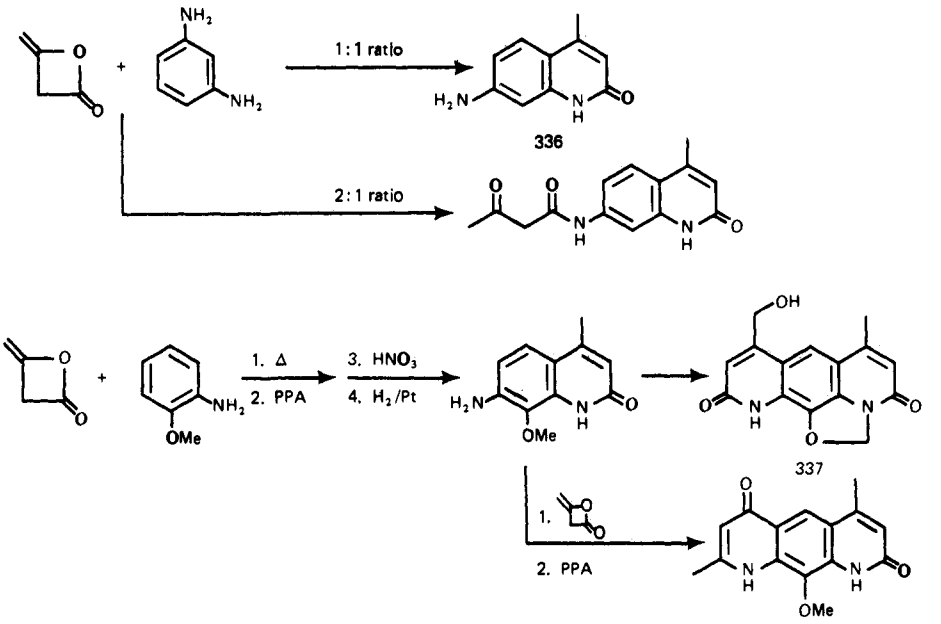

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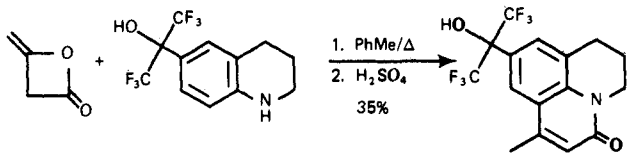
SCHEME CL



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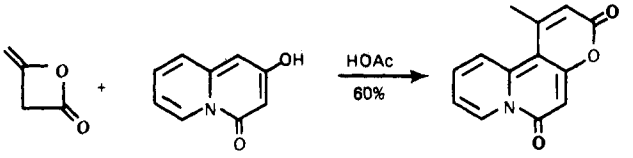

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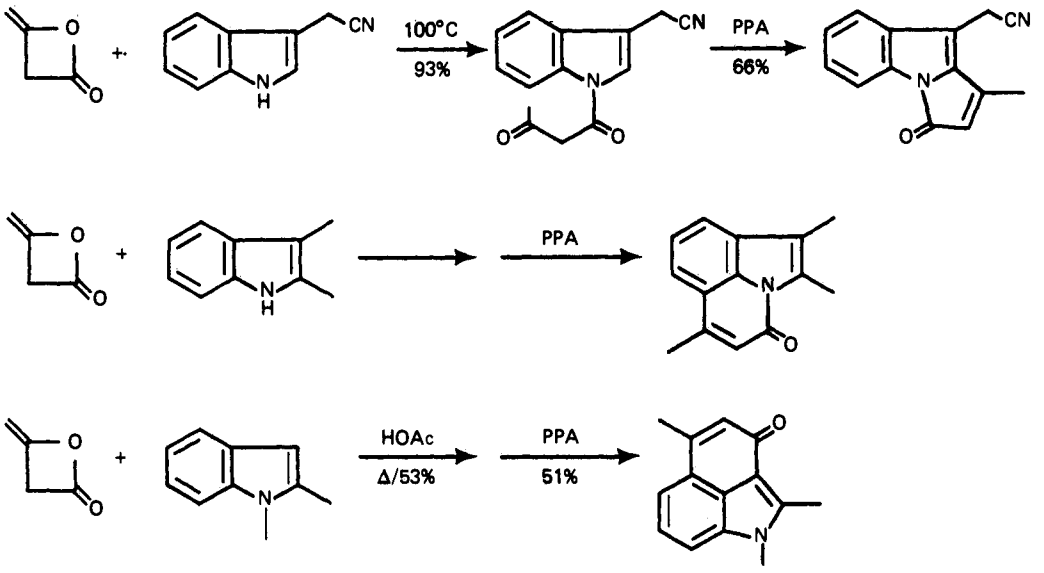

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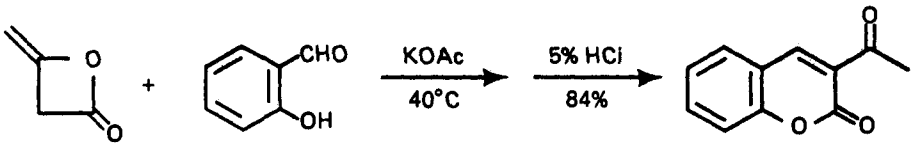

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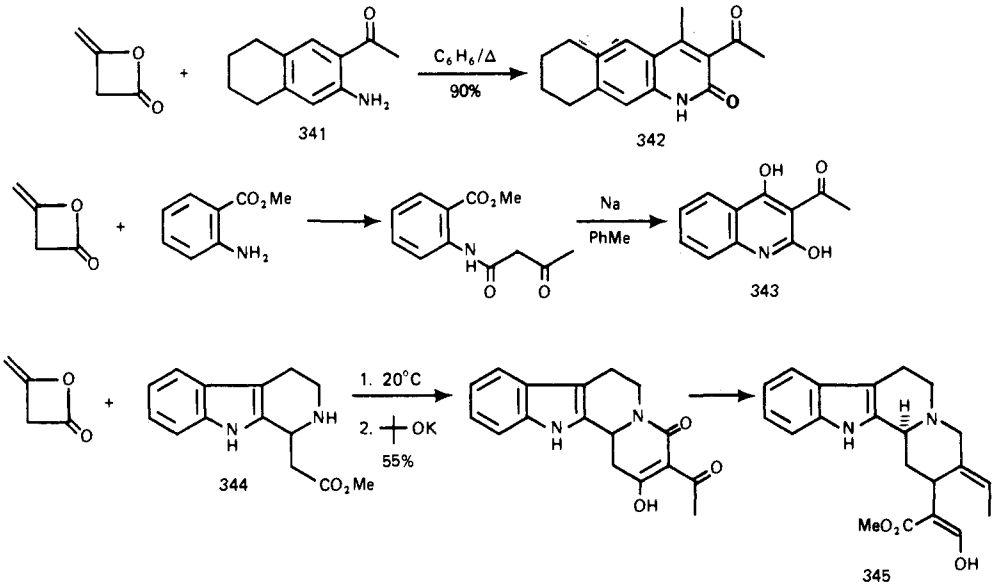
SCHEME CLIV



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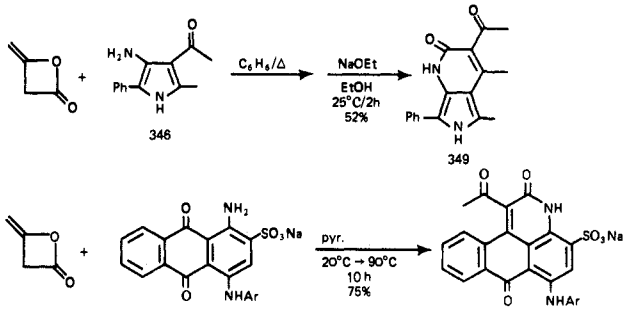
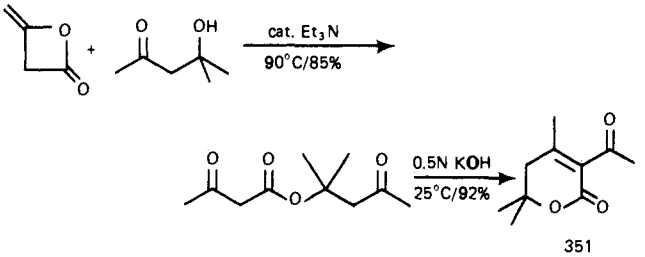


SCHEME CLVI



Büchi cyclized *N*-acetoacetyl-*S*-benzyl-L-cysteine ethyl ester enroute to the antibiotic holomycin (**404**)[483] (Scheme CLXXIX). The reaction of diketene with an α-amino ester has been used in a synthesis of the mycotoxin DL-β-cyclopiazonic acid (**405**);[464] the synthesis of α-cyclopiazonic acid (**406**) has recently been described and uses diketene in a similar manner.[485] Other substituted pyrrolidine-2,4-diones (tetramic acids, e.g., **407**) have been used as precursors for the preparation of naturally occuring antibiotics such as streptolydigin and the tirandamycins.[486]

As would be expected, α-amino amides and α-amino nitriles can also be used to prepare pyrrolidinone derivatives. In the case of the α-amino amides, anilides

SCHEME CLVII

afford different products (**408**) than are obtained (**409**) with aliphatic N-substituents[487] (Scheme CLXXX). The acetoacetamide of aspartimide **410** rearranges to a tetramic acid derivative.[488] α-Amino nitriles can be used to prepare aminopyrrolinones such as **411**.[489] Azahomoadamantane **412** reacts with diketene to afford a fused ring system (**413**).[490]

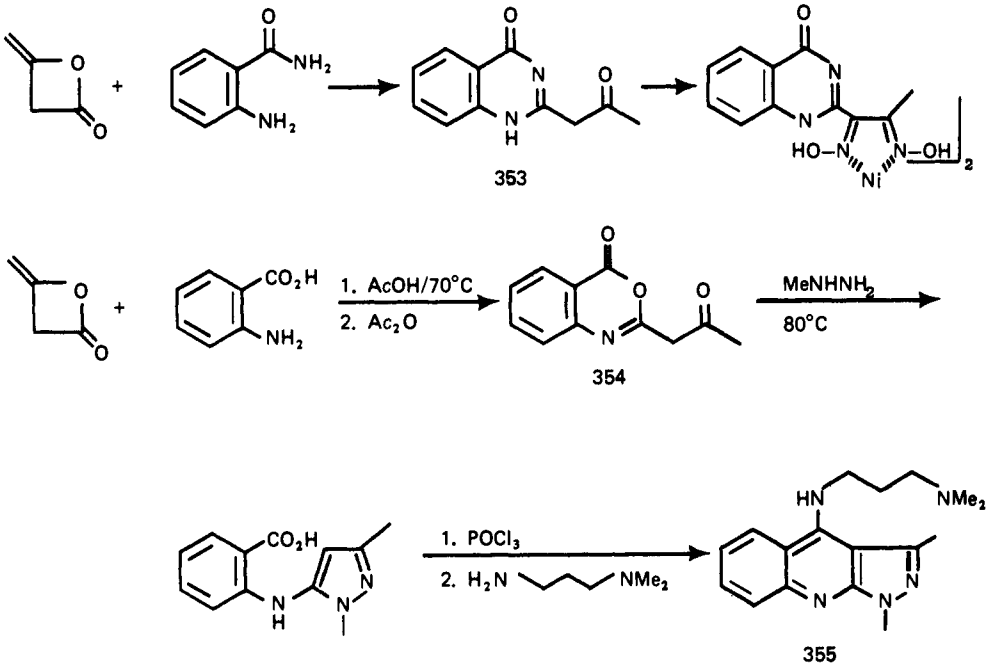
The reactions of aminotropones and aminotropolones with diketene have been extensively studied.[491] In the presence of a stoichiometric quantity of diketene, acetoacetamidotropones and -tropolones are readily prepared (Scheme CLXXXI). With excess diketene, mixtures of pyrone and pyridone derivatives are formed as a result of further condensation of the aminotropolone acetoacetate with diketene;[492] the composition of the product mixtures was found to be dependent on the acidity of the aminotropone.[493] 2-Acetoacetamidotropones undergo ring closure to give cyclohepta[*b*]pyrrole derivatives,[492] such as the aldose reductase inhibitor **414**.[494]

Acetoacetamides have been nitrosated and converted into α-aminoacetoacetamides which were used for the preparation of a series of herbicidal pyrroles (e.g. **415**) (Scheme CLXXXII); conversely, the acetoacetic ester could be nitrosated and reductively condensed with an acetoacetamide.[495]

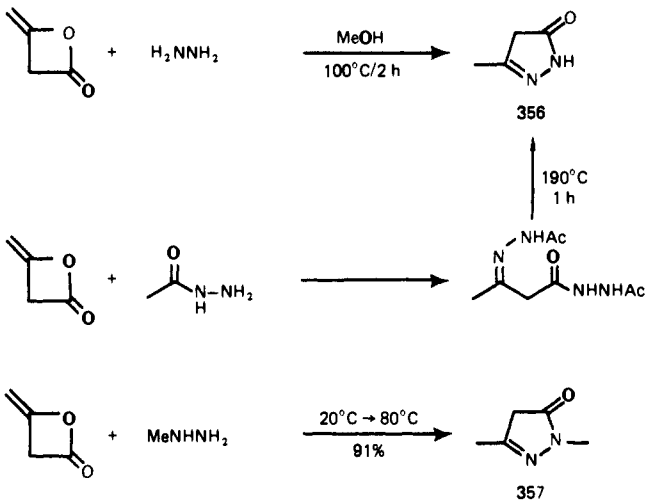
E. Heterocycles Derived from Haloacetoacetates

Haloacetoacetate esters derived from diketene are frequently used in heterocyclic synthesis; several il-

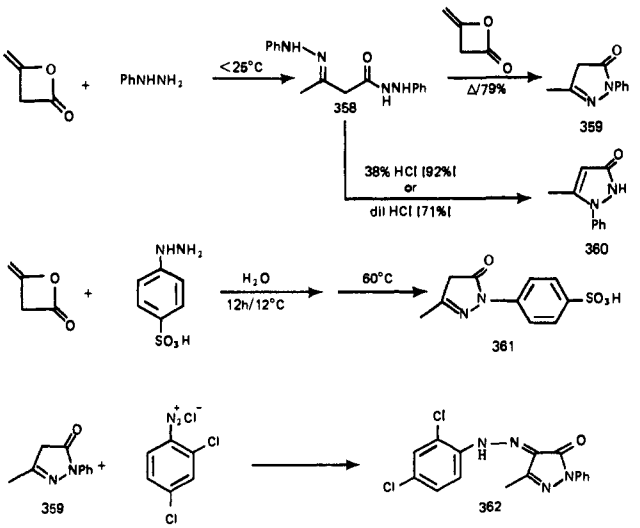
SCHEME CLVIII



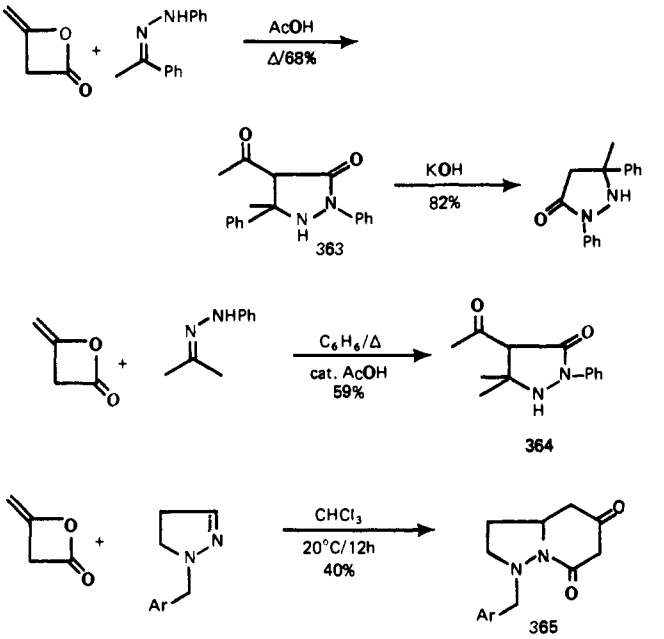
SCHEME CLIX



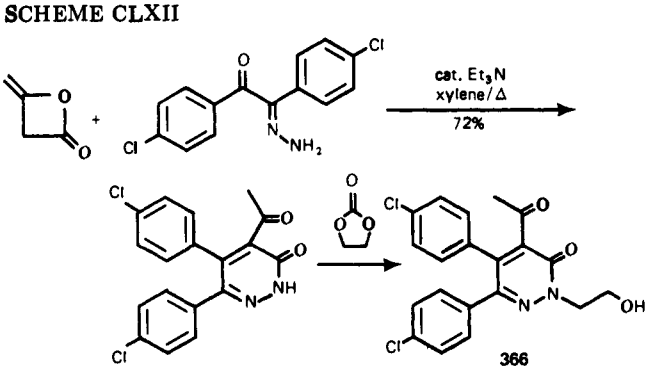
SCHEME CLX



SCHEME CLXI



SCHEME CLXII



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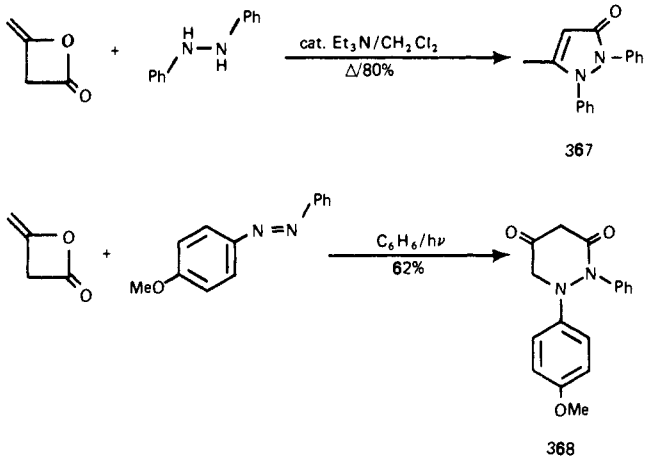

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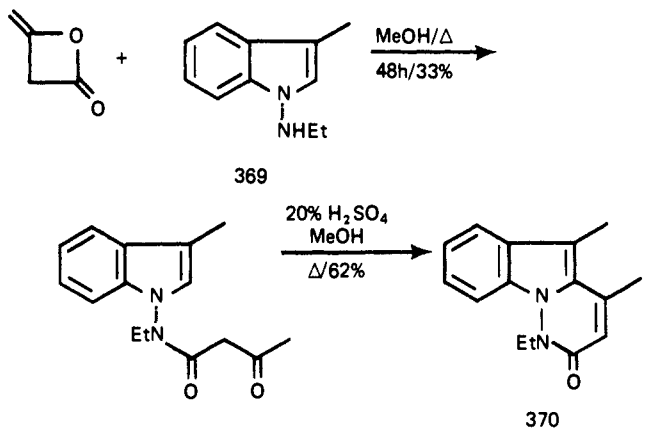

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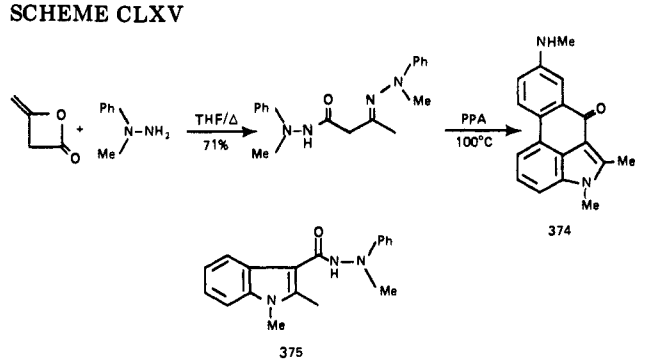
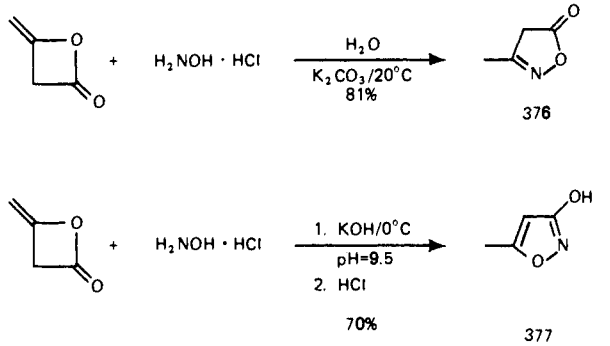


SCHEME CLXVI



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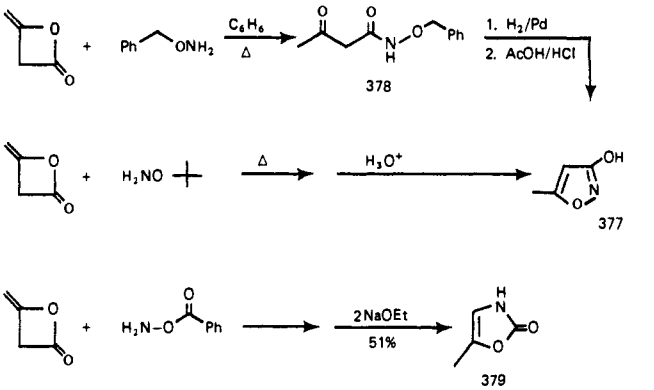

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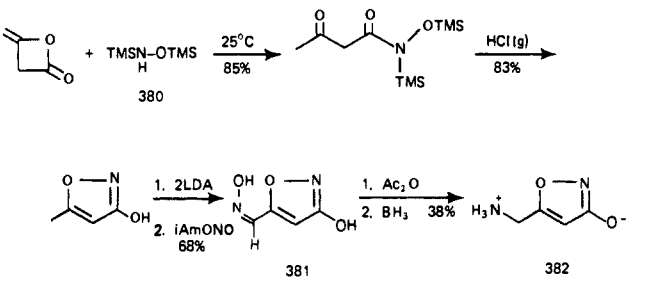

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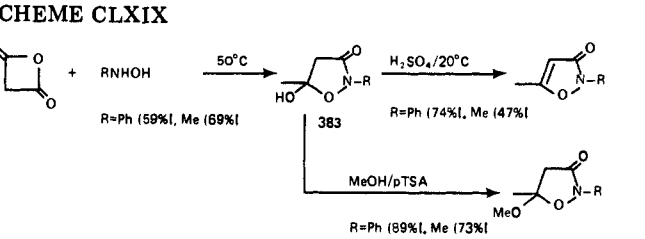

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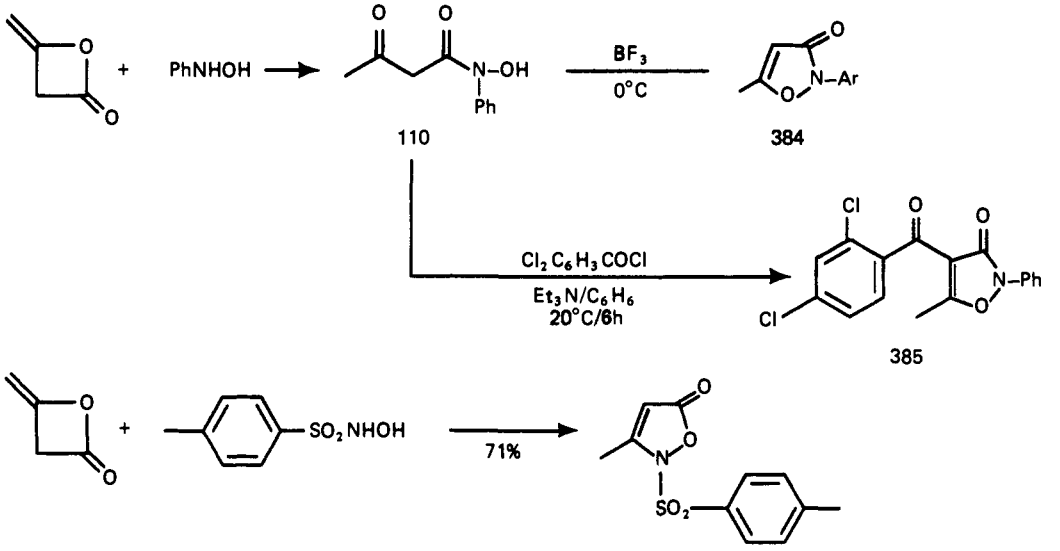

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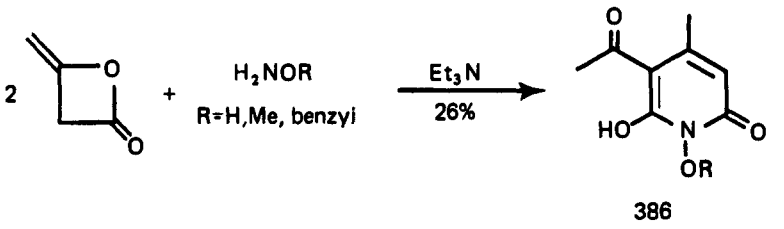

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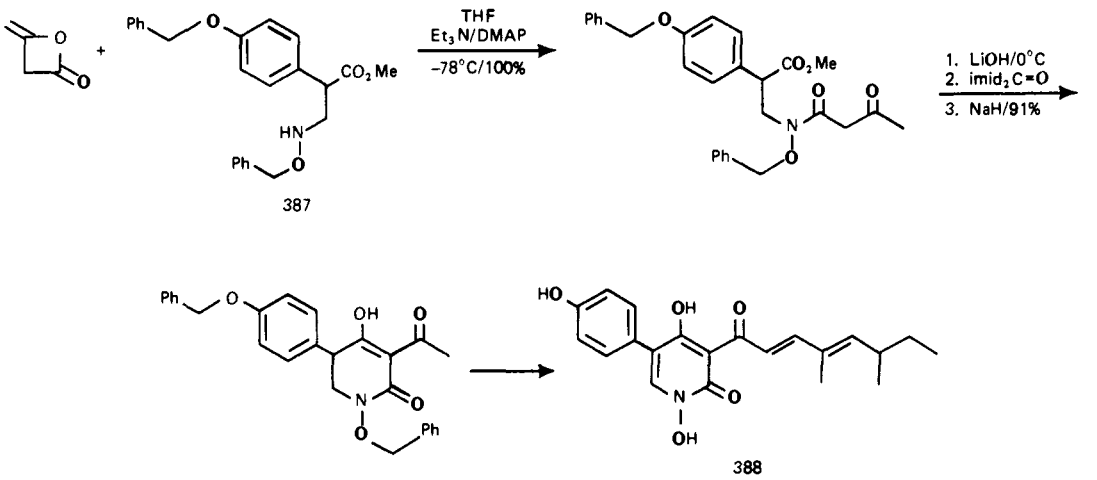

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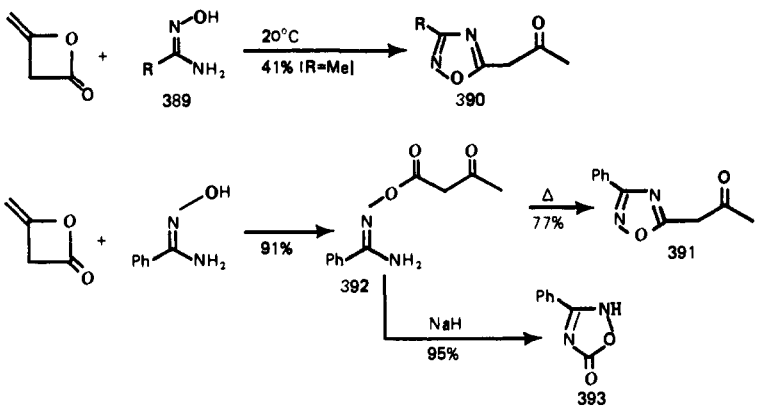

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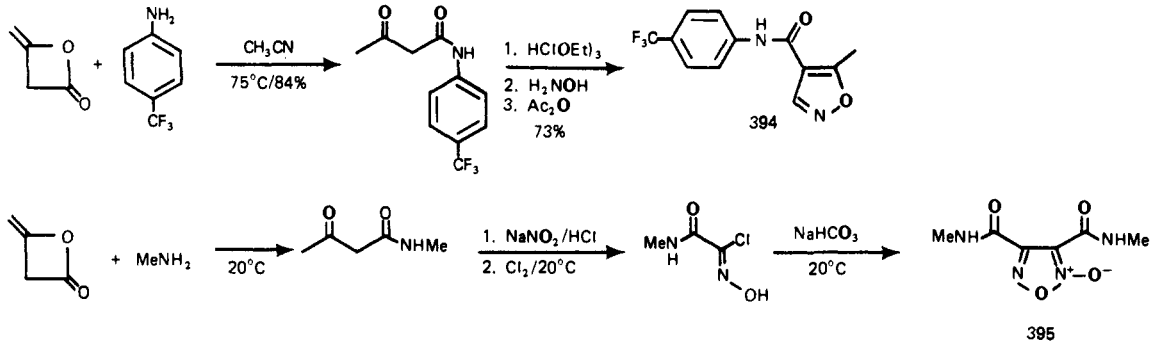

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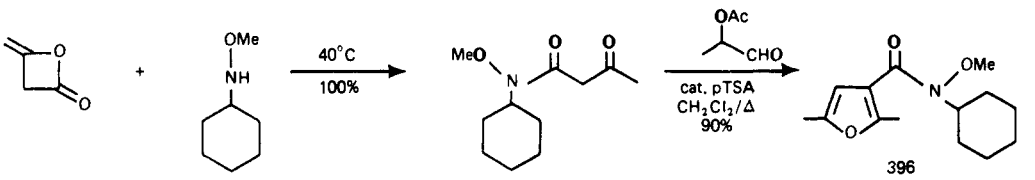

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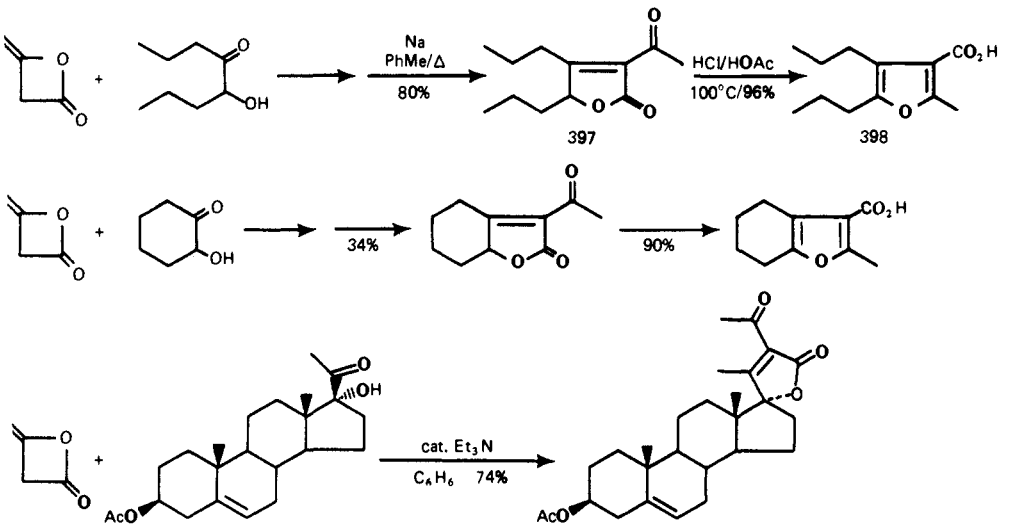

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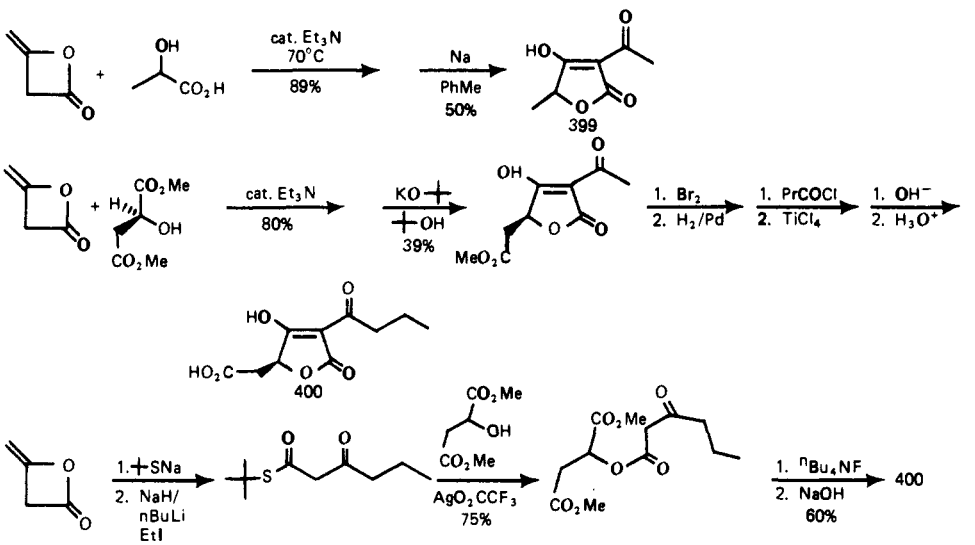
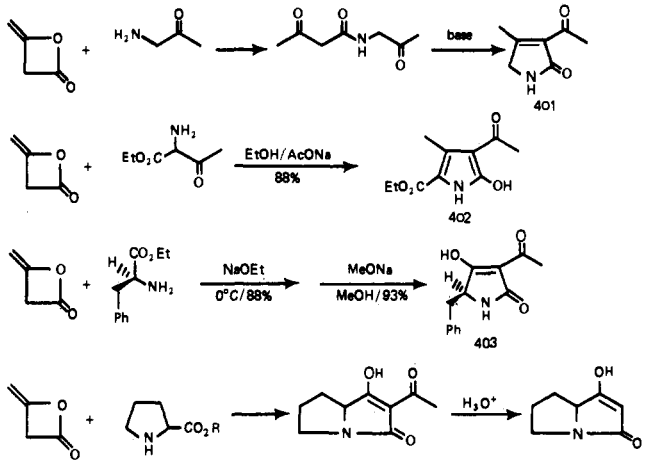


SCHEME CLXXVIII



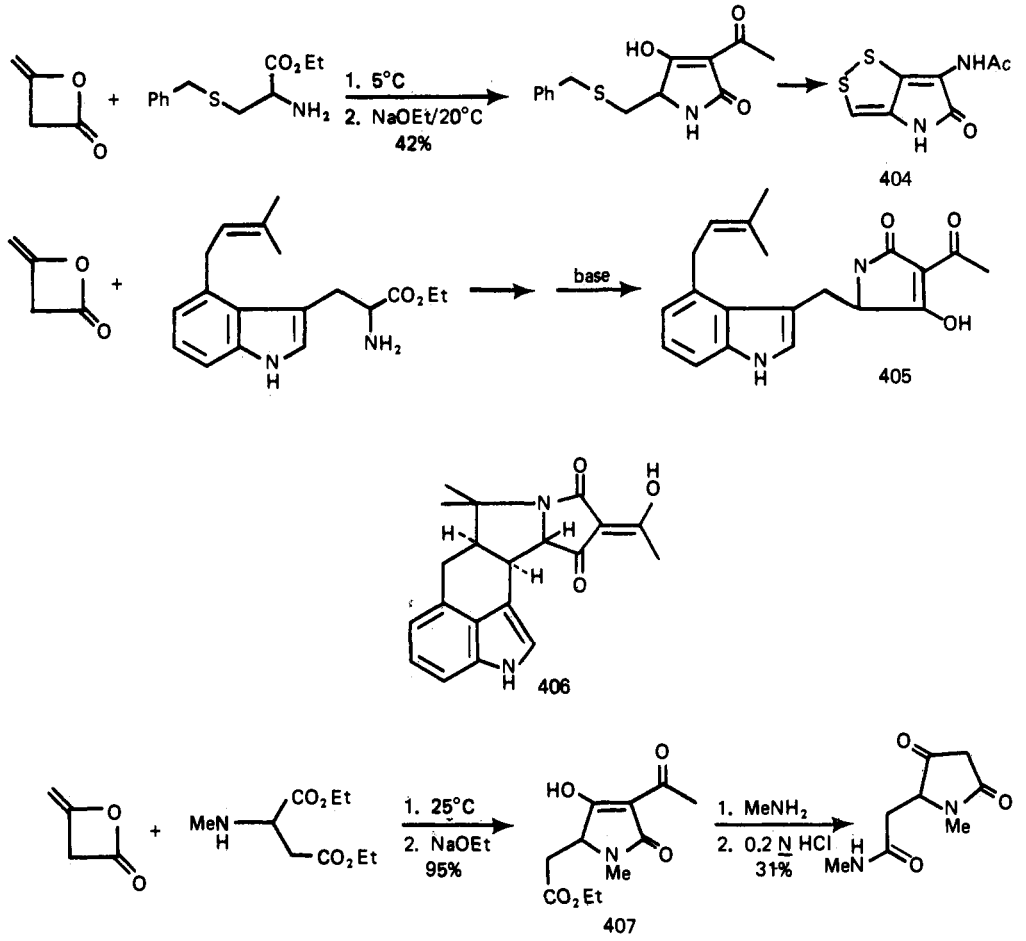
ridoxine can be made from 2-chloroacetoacetamide in formic acid/formamide at moderate temperature;[496] further heating results in the formation of imidazoles (417) from the same reactants (Scheme CLXXXIII). This latter imidazole synthesis has been used in the preparation of antisecretory compounds, such as cimetidine[497] and its analogues.[498]

The thiazole 418, which results from vitamin B_1 degradation, has been prepared from 2-chloroacetoacetate esters and thioformamide[499] (Scheme CLXXXIV). Another thiazole (419) derived from diketene is a patented antisecretory agent.[500]

Aminofuran 420 and cyanopyrrole 421 can be prepared from ethyl 2-chloroacetoacetate and the sodium salt of acetoacetonitrile[501] (Scheme CLXXXV).

The reaction of 2-chloroacetoacetic acid derivatives with diazonium salts provides oxalyl chloride derivatives

SCHEME CLXXIX

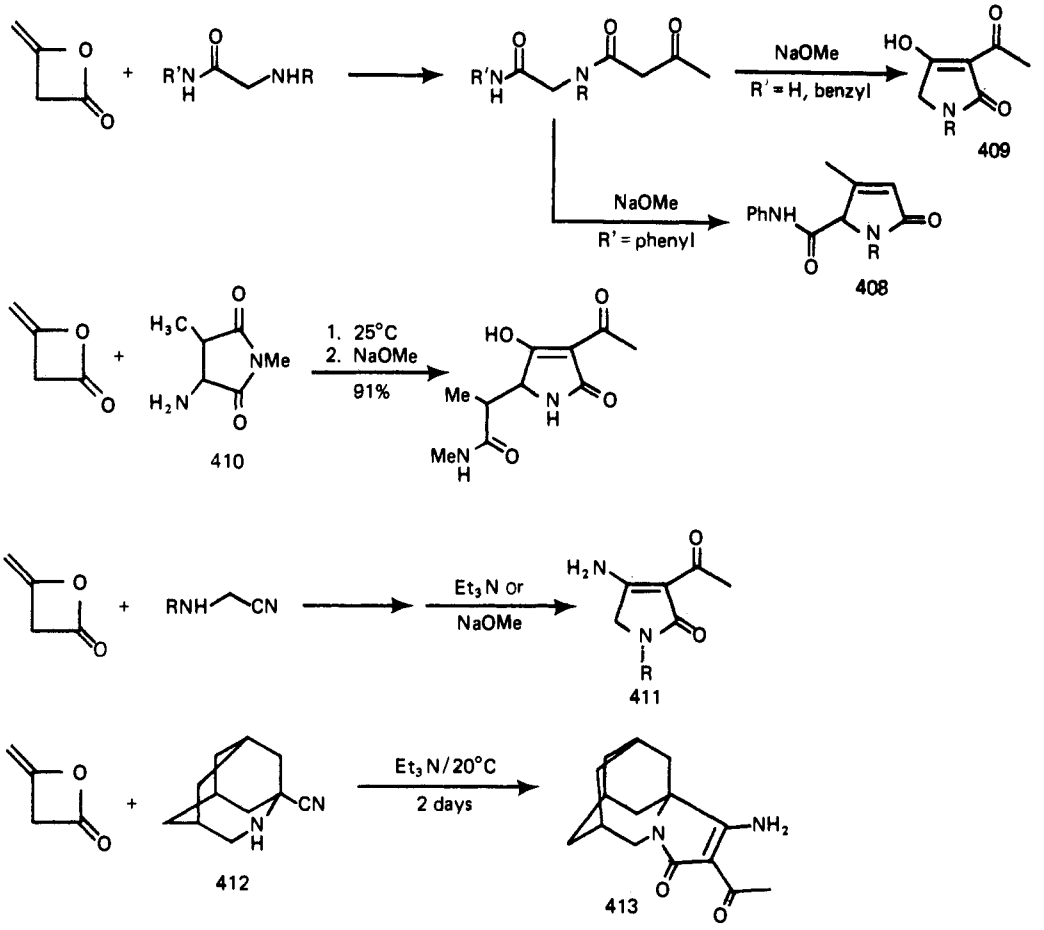


lustrative examples follow. 2-Chloroacetoacetic acid derivatives are commonly used intermediates for the preparation of five-membered heterocycles, such as oxazoles, imidazoles, and thiazoles. In virtually every example of heterocyclization in which a 2-chloroacetoacetic acid derivative is utilized, the carbons at the 2- and 3-positions are incorporated into the heterocyclic nucleus and the product contains a pendant methyl group. Thus, the oxazole (416) used for preparing py-

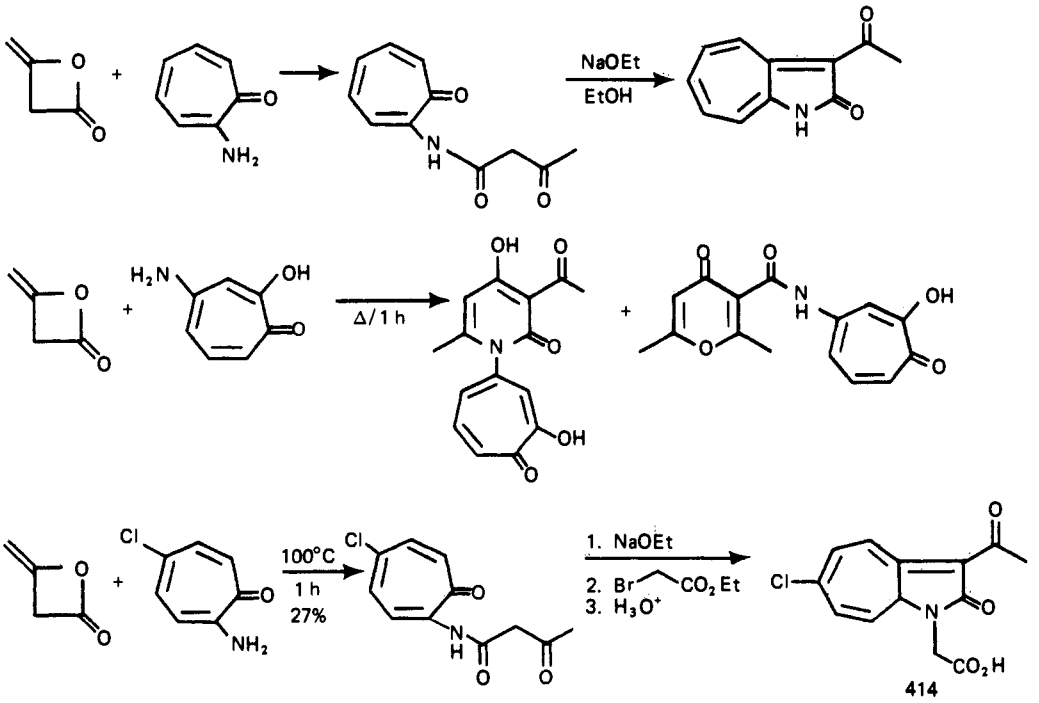
(e.g., 423) which are useful intermediates for the preparation of pyrazoles[71] (Scheme CLXXXVI). In one such application, *N*-propargylacetoacetamide was converted into the pyrrolopyrazole 422 via the nitrile imine generated from 423.[71b]

The fungicide carboxin (424) provides an example of a six-membered heterocycle accessible from 2-haloacetoacetates.[502] Likewise, L-cysteine ethyl ether ester has been treated with ethyl 2-chloroacetoacetate (and

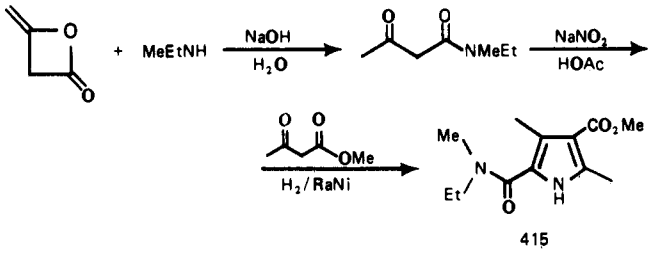
SCHEME CLXXX



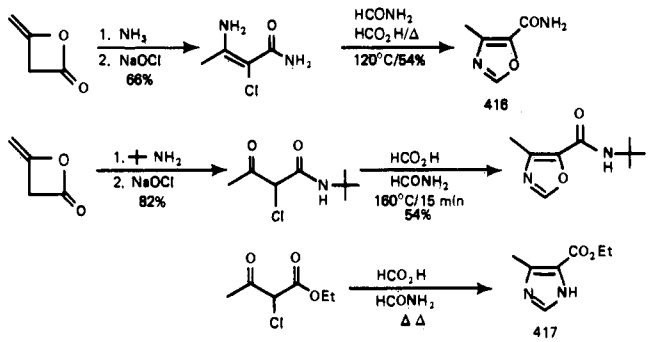
SCHEME CLXXXI



SCHEME CLXXXII



SCHEME CLXXXIII



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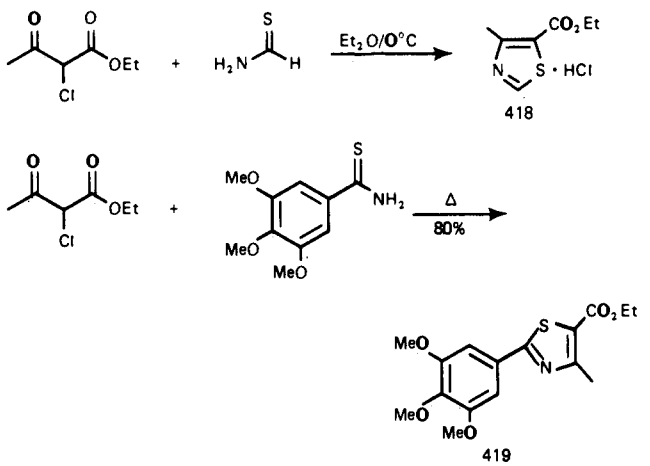
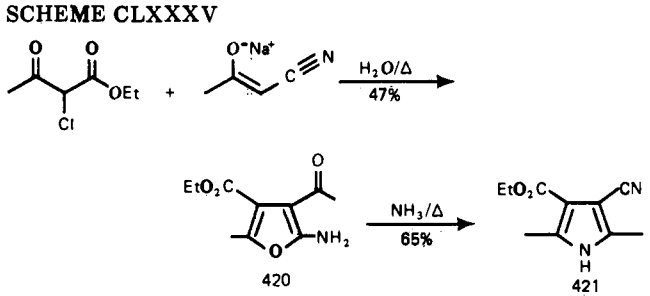


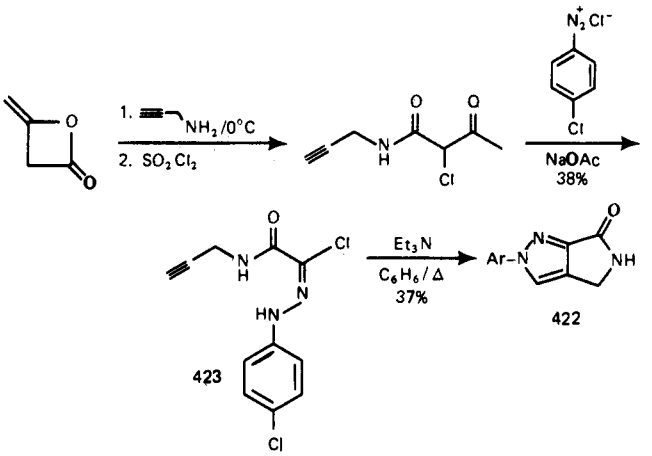
SCHEME CLXXXV



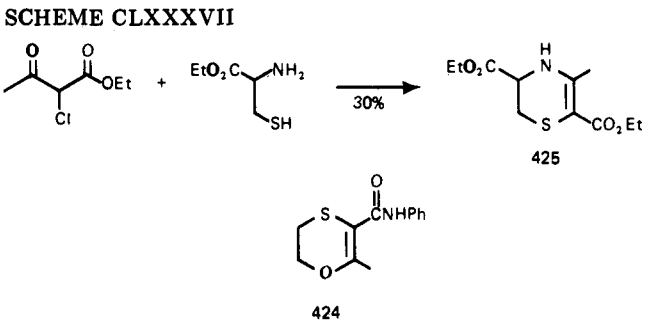
several 2-chloroacetoacetamides) to form 1,4-thiazidines, such as **425**[503] (Scheme CLXXXVII).

In general, 2-bromoacetoacetates are less stable than chloroacetoacetates and are seldom used in organic synthesis. However, an alkylative sulfide contraction of thioamide **427**, prepared from ethyl 2-bromoaceto-

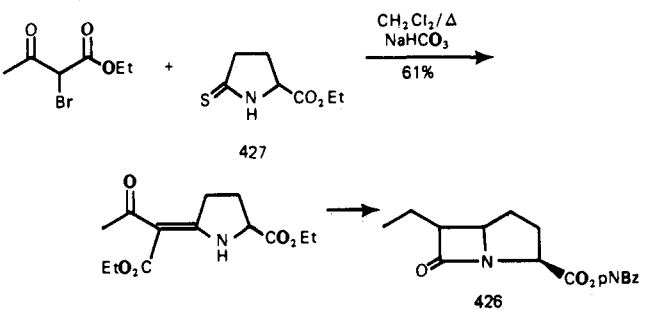
SCHEME CLXXXVI



SCHEME CLXXXVII



SCHEME CLXXXVIII

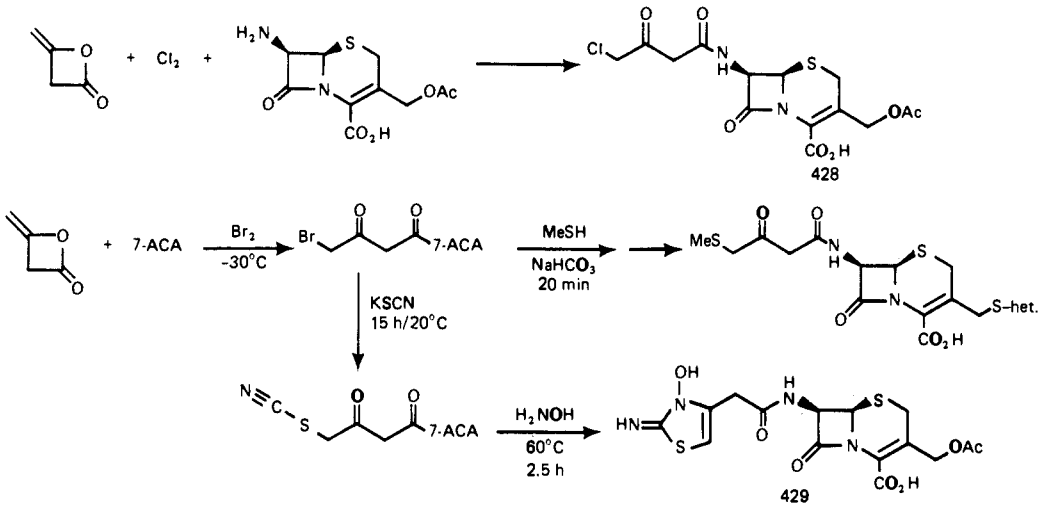


acetate, has recently been used to make carbapenam **426**[504] (Scheme CLXXXVIII).

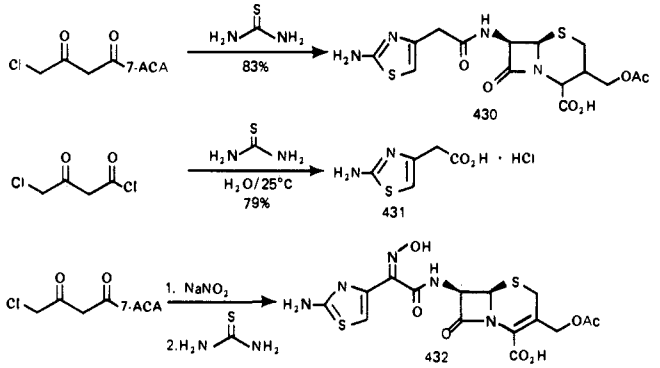
4-Haloacetoacetate esters undergo at least three different types of heterocyclization reactions. In the first type, ring closure occurs on the halogen and the keto group, while in the second type the halogen remains intact and cyclization occurs on the ester and keto groups of the acetoacetate. This latter type of cyclization is important to diketene chemistry because it facilitates the preparation of compounds without a pendant methyl group. In the third type of heterocyclization, the halogen is converted into a hydroxyl group and the molecule is lactonized to afford a tetronic acid.

Diketene is used extensively for the preparation of substituted acetoacetamido side chains for β-lactam antibiotics, and most of these heterocyclizations fall into the first of the aforementioned reaction types. Thus, 4-(chloroacetoacetamido)cephalosporanic acid (**428**), prepared from chlorine, diketene, and 7-aminocephalosporanic acid (7-ACA) (Scheme CLXXXIX), ex-

SCHEME CLXXXIX

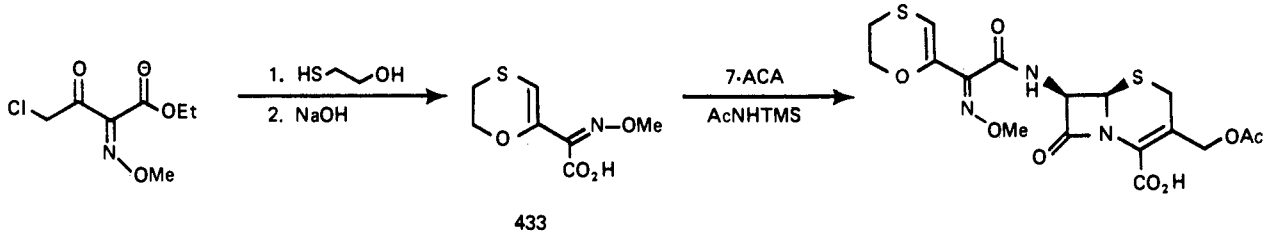


SCHEME CXC



hibits modest antibiotic activity.[505] More active side chains have been introduced by displacement of the side chain halogen or by ring closure of the resulting adducts (e.g., **429**).[506] Conversion of 4-haloacetoacetamido side chains into aminothiazoles with thiourea has been used to prepare several antibiotics with outstanding activity (c.f. **430**)[507] (Scheme CXC). This aminothiazoleacetic acid side chain (**431**) is also prepared separately for attachment to other β-lactams.[508] Another common

SCHEME CXCI



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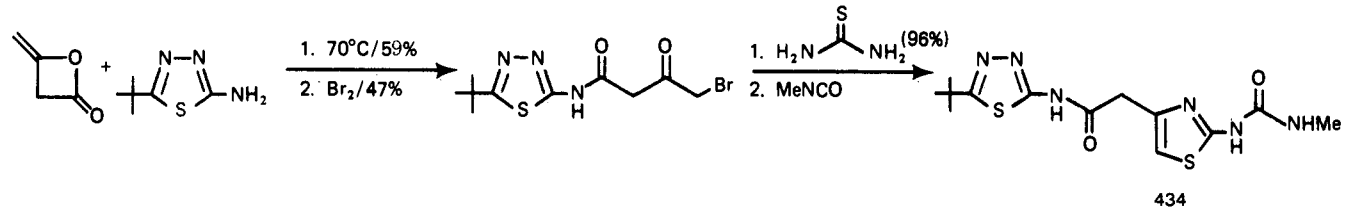

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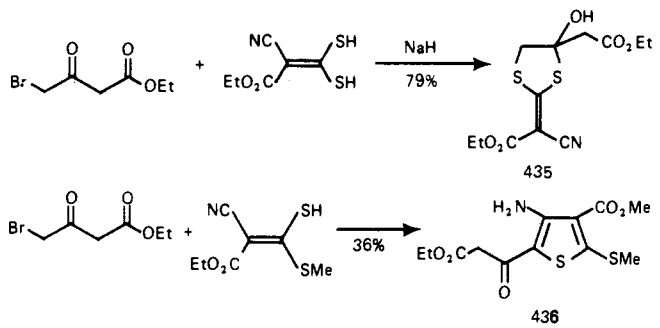

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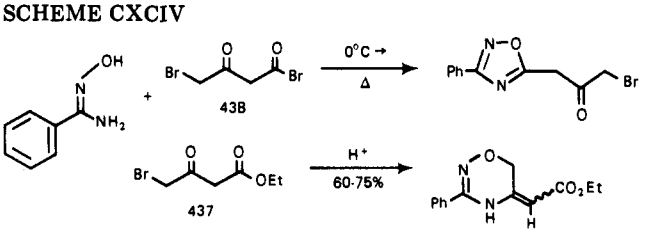
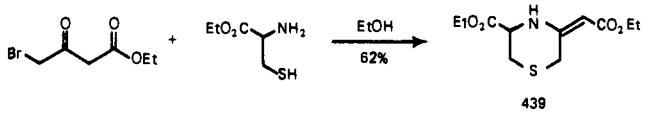
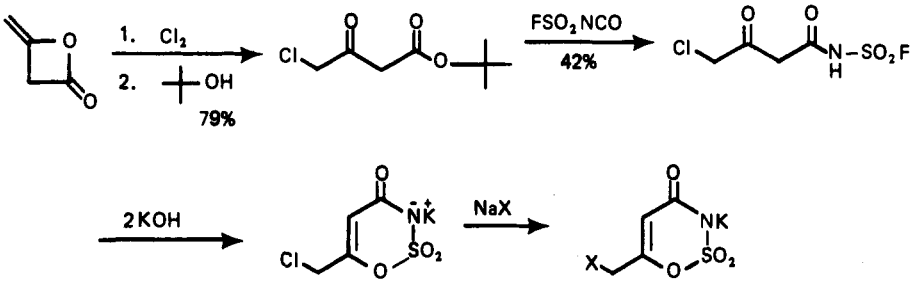


SCHEME CXCV

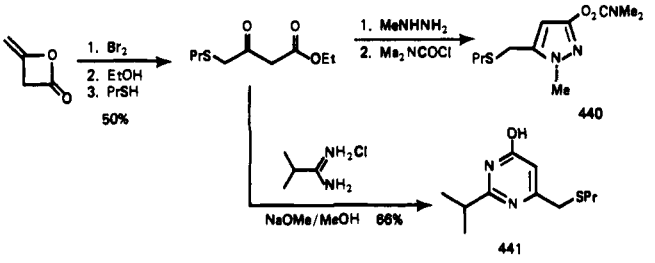


439

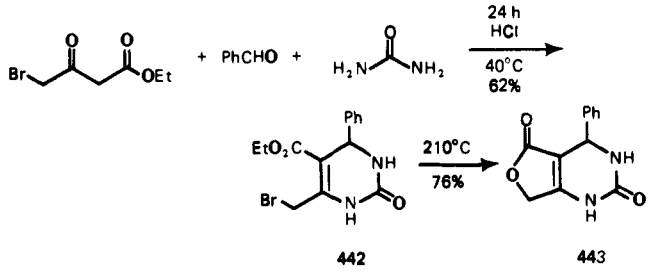
SCHEME CXCVI



SCHEME CXCVII



SCHEME CXCVIII



β-lactam side chain (c.f. **432**) is prepared via nitrosation of the active methylene group of 4-haloacetoacetamides prior to cyclization with thiourea.[509]

Methylation of the oxime affords yet another series of active compounds.[510] Other heterocycles, such as **433**, have also been attached to 7-ACA via diketene chemistry[511] (Scheme CXCI).

The functionalized aminothiazole **434**, prepared from 4-haloacetoacetates, is claimed to be a post-emergent herbicide.[512] It should be noted that the 4-bromoacetoacetate intermediate used to make **434** was prepared by the facile thermal isomerization of the 2-bromo isomer (Scheme CXCII).

The reaction of ethyl 4-bromoacetoacetate with cyanoethenedithiols to form **435** and **436** has been explored[513] (Scheme CXCIII).

The outcome of a reaction can be influenced by the acetoacetic acid derivative used. The different reactivities of the ester **437** and the acid bromide **438** toward benzohydroxamide facilitated the preparation of two completely different products[514] (Scheme CXCIV).

The ethyl ester of L-cysteine reacts with ethyl 4-bromoacetoacetate to afford the 1,4-thiazidine **439**[503] (Scheme CXCV).

Examples of the second type of 4-haloacetoacetate heterocyclization, in which the halogen remains intact, are also fairly common. Sweet-tasting analogues of the artificial sweetener acesulfame K (**116**) have been prepared from diketene via ring closure of the enolate of a 4-chloroacetoacetamide[515] (Scheme CXCVI).

Hydrazines have been used to prepare herbicidal pyrazoles (**440**) from 4-substituted acetoacetates[516] (Scheme CXCVII). In this instance, the halide was displaced prior to cyclization. Similarly, amidines have been used to prepare analogues (**441**) of diazinon from 4-bromoacetoacetates.[517]

A recent synthesis of pyrimidone derivatives **442** and **443** provided yet another example in which the halomethyl group was carried through the heterocyclization and then utilized in a subsequent reaction[518] (Scheme CXCVIII).

4-Chloroacetoacetates are precursors to tetronic acid **444**, via 4-alkoxy and 4-hydroxyacetoacetate intermediates[519] (Scheme CXCIX). Closely related is the chiral synthesis of (−)-4-hydroxypyrrolidin-2-one (**445**), a natural product isolated from *Amanita muscaria*.[520]

F. Miscellaneous

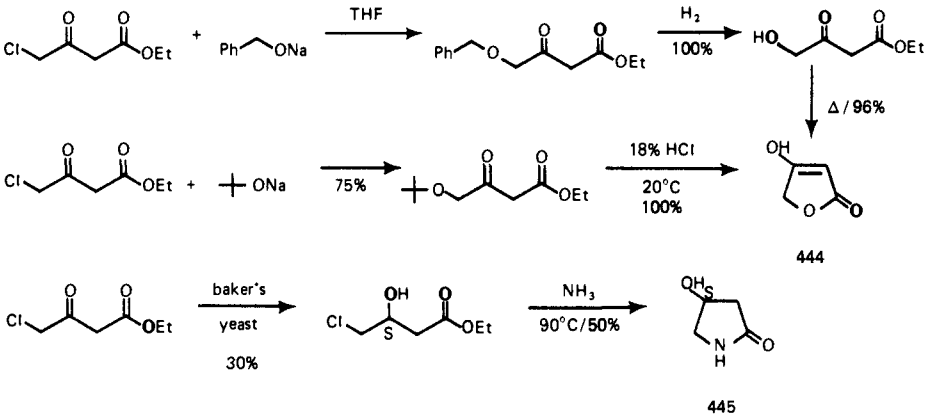
Diketene reacts with sulfonium ylides to give furanones.[521] Thus, acyl dimethylsulfonium methylides **446** and **447** are acylated with diketene, and the resulting enolates displace dimethyl sulfide to afford 2-acyl-3-hydroxy-5-methylfuran **448** and the spirocyclic furanone **449**, respectively[522] (Scheme CC). Isoquinolinium ylide **450** is similarly acetoacetylated with diketene but undergoes ring closure via the carbon terminus of the enolate intermediate to afford **451**.[523] Sulfilimine ylides react with diketene to afford new ylides (**452**), presumably via a four-membered cyclic intermediate.[524]

Isonitriles react with diketene to afford highly functionalized butenolides (**453**) (Scheme CCI), which are useful as aging inhibitors for rubber.[525]

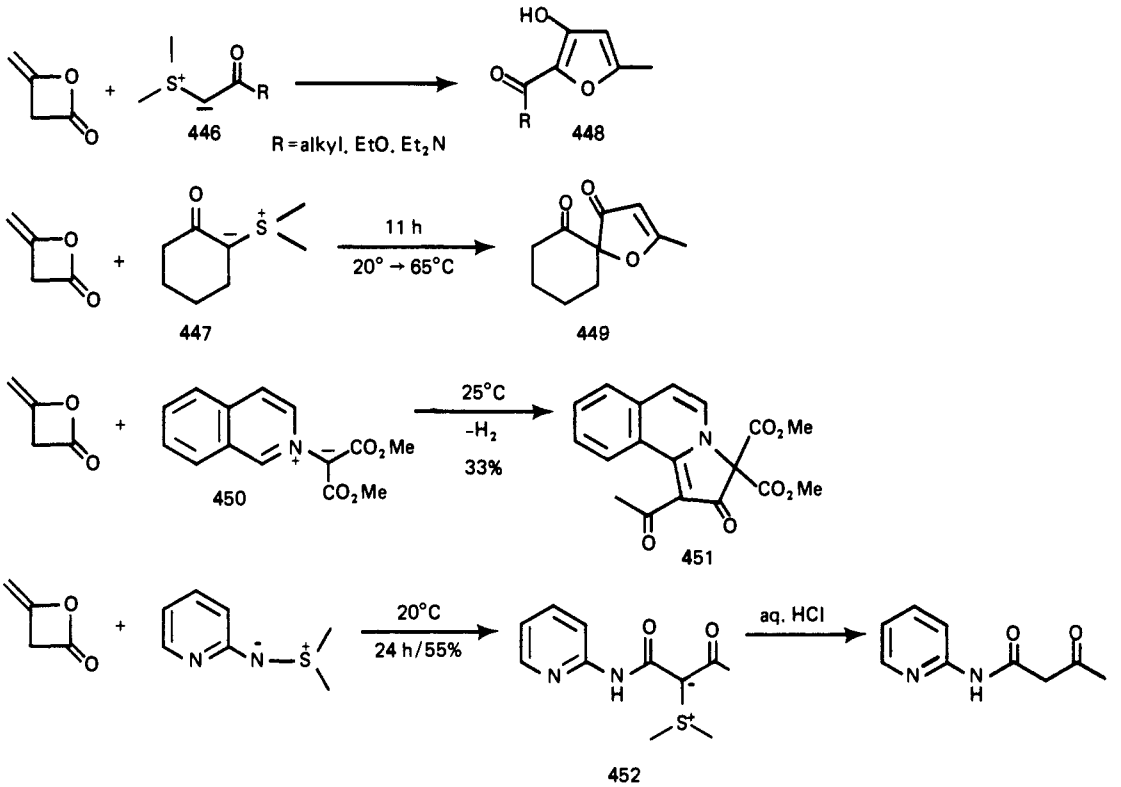
Allylamine is readily converted into *N*-allylacetoacetamide with diketene,[246] and this adduct can be cyclized into 2-acetonyloxazoline **456**[526] (Scheme CCII). Other amines react similarly to provide substituted oxazolines. Alternately, 2-hydroxyethyl amines can be acetoacetylated with diketene and cyclized into oxazolines upon treatment with thionyl chloride at reflux. Acetoacetylated aziridines also rearrange to oxazolines.[527]

The reaction of 2-mercaptoaniline with diketene in benzene provides one major product, but two different structures have been ascribed to this compound

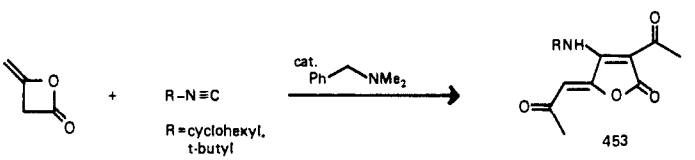
SCHEME CXCIX



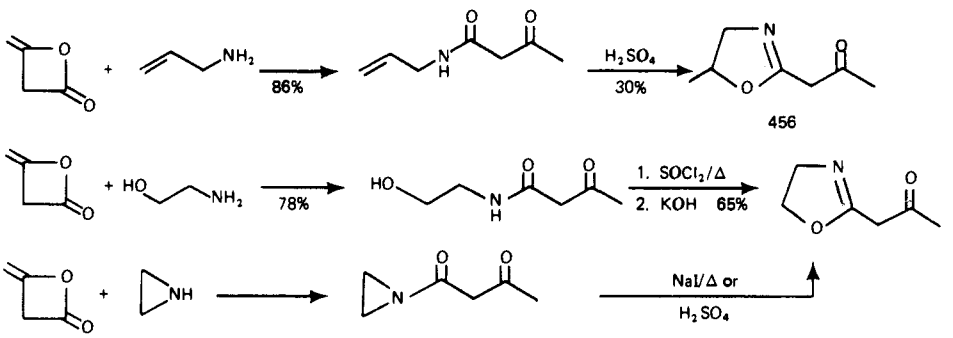
SCHEME CC



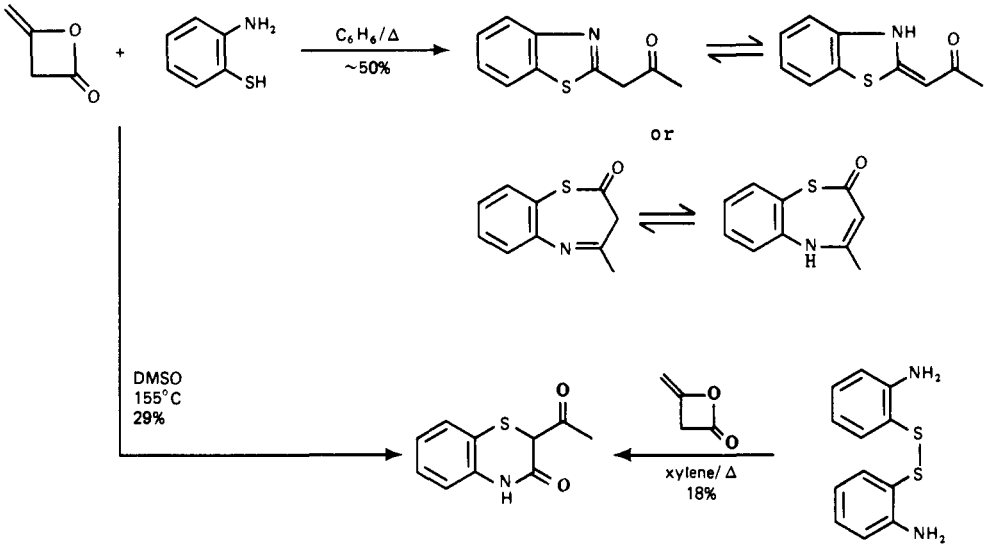
SCHEME CCI



SCHEME CCII



SCHEME CCIII



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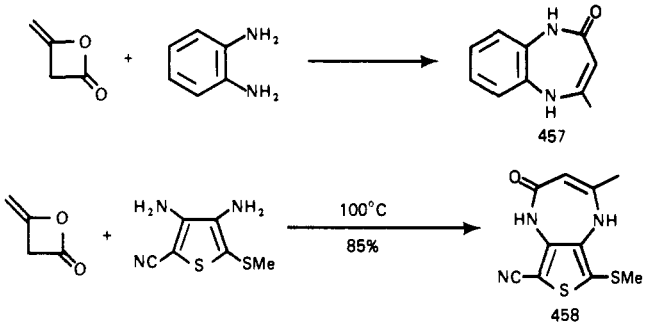
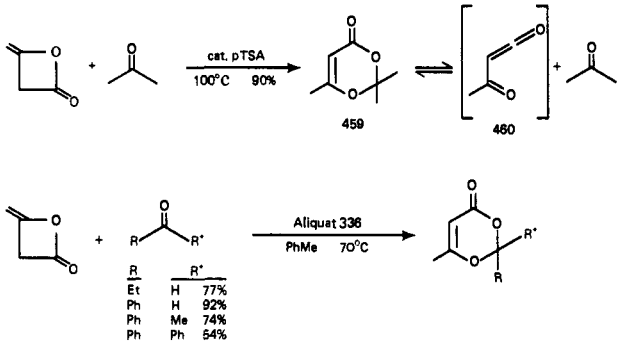


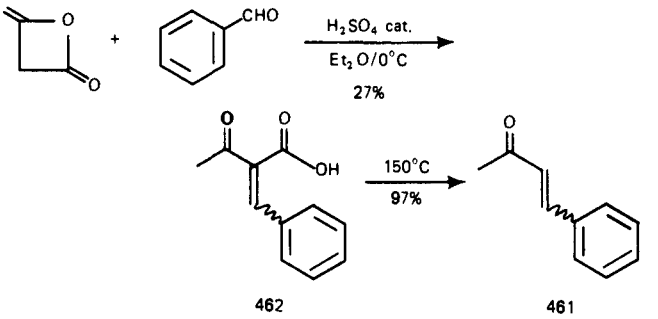
SCHEME CCV



(Scheme CCIII); the available chemical and spectral data is ambiguous, and further research is warranted.[397,528] In hot dimethyl sulfoxide, diketene reacts with 2-mercaptoaniline to afford a benzothiazinone, via an intermediate disulfide.

Diketene condenses with *o*-phenylenediamine to provide diazepinone **457**;[529] other *o*-diaminoheterocycles provide analogous fused diazepinones (**458**)[530] (Scheme CCIV). Diazepinones have also been prepared from *o*-nitroanilines and diketene via an acetoacetylation/reduction/ring-closure sequence.[531]

SCHEME CCVI



VI. Other Reactions of Diketene

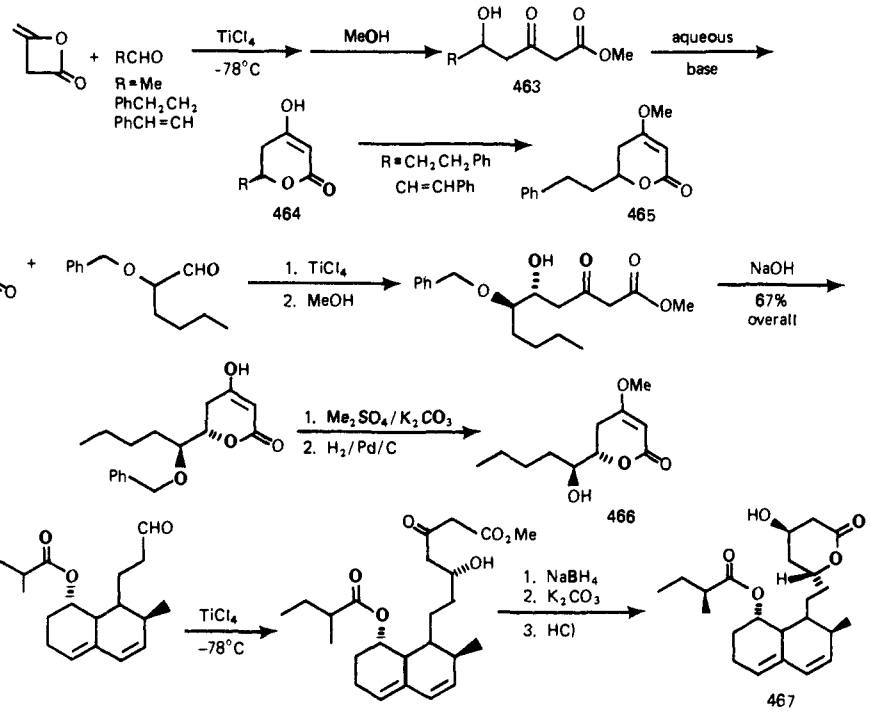
A. Reactions with Carbonyl Compounds

Diketene reacts with carbonyl compounds to produce several types of adducts, such as 2- and 4-substituted acetoacetates and 1,3-dioxin-4-ones. Thus, in the presence of *p*-toluenesulfonic acid, diketene reacts with acetone to afford 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**459**)[532] (Scheme CCV). A number of analogous 1,3-dioxin-4-ones have been similarly prepared from other aromatic and aliphatic ketones[533] and aldehydes.[534] In addition to acidic catalysts, zinc sulfate in pyridine,[535] a palladium(II) complex,[74b] and a quaternary amine resin[536] have also been used to catalyze dioxinone formation. The product that resulted from the reaction catalyzed by zinc sulfate was incorrectly identified as isopropenyl acetoacetate.

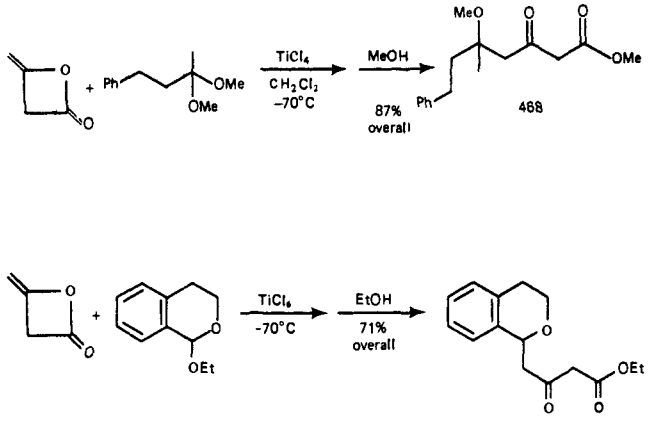
The diketene/acetone adduct **459** is an extremely useful diketene derivative. The physical properties and the handling characteristics of this adduct are similar to those of methyl acetoacetate, but the reactions more closely resemble those of diketene.[537] Upon pyrolysis, **459** provides acetylketene (**460**), which is useful for acetoacetylation and cycloaddition reactions.[538] In general, the chemistry of other 1,3-dioxin-4-ones has not been extensively investigated.

Diketene reacts with benzaldehyde in the presence of sodium acetate to give benzalacetone (**461**)[14] (Scheme CCVI). When benzaldehyde and diketene are reacted under acidic conditions, the benzylideneacetoacetic acid intermediate **462** can be isolated and then readily decarboxylated to benzalacetone.[539] Cinnamaldehyde reacts similarly.

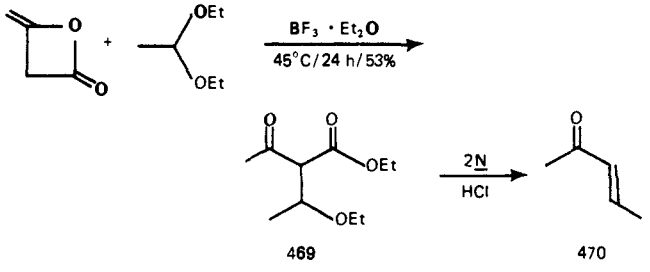
SCHEME CCVII



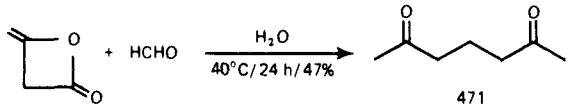
SCHEME CCVIII



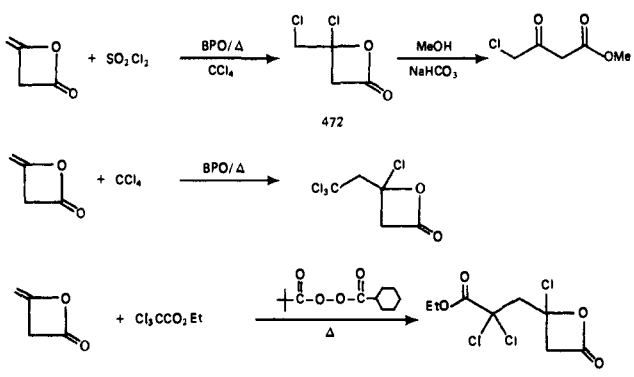
SCHEME CCIX



SCHEME CCX



SCHEME CCXI



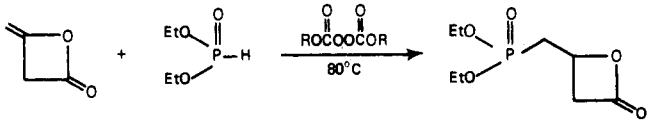
The titanium tetrachloride catalyzed reaction of diketene with aldehydes provides 4-substituted acetoacetates **463**,[540,541] which are readily cyclized under basic conditions to give 6-substituted 4-hydroxy-5,6-dihydro-2-pyrones (**464**)[540] (Scheme CCVII). This reaction has been used in the synthesis of kawains (**465**),[540] (±)-pestalotin (**466**),[541] compactin (**467**),[542] and a series of postemergent herbicides.[543]

In a closely related reaction, diketene reacts with acetals and ketals in the presence of titanium tetrachloride to produce 4-substituted acetoacetates, such as **468** (Scheme CCVIII). This reaction provides a good alternative to dianion chemistry for producing acetoacetic esters that are functionalized at C-4.[544]

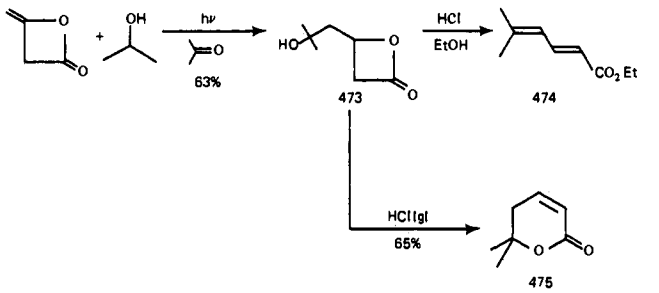
Surprisingly, the use of catalytic amounts of boron trifluoride in place of stoichiometric quantities of titanium tetrachloride in the above reaction of acetals with diketene yields 2-substituted acetoacetates (**469**)[545] (Scheme CCIX). Upon treatment with acid, these latter compounds can be converted into methyl vinyl ketones (**470**).

Diketene reacts with aqueous formaldehyde to provide 2,6-heptanedione (**471**)[546] (Scheme CCX).

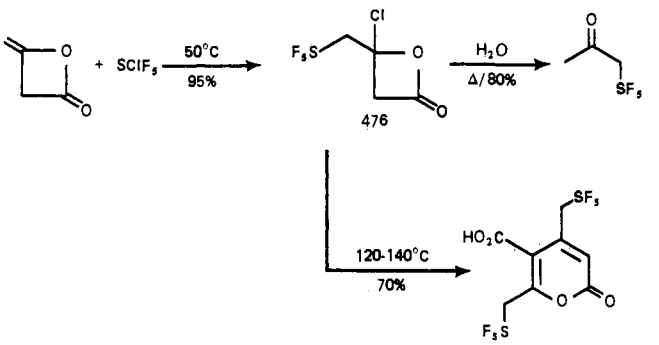
SCHEME CCXII



SCHEME CCXIII



SCHEME CCXIV



C. Reactions of the Exocyclic Double Bond of Diketene

There is a series of diketene reactions in which the exocyclic double bond of diketene reacts, but the β-lactone ring remains intact.[3a,547] Almost all the reactions of the exocyclic olefin in diketene can be categorized as radical addition reactions, carbene or nitrene additions, or photochemical [2 + 2] reactions.

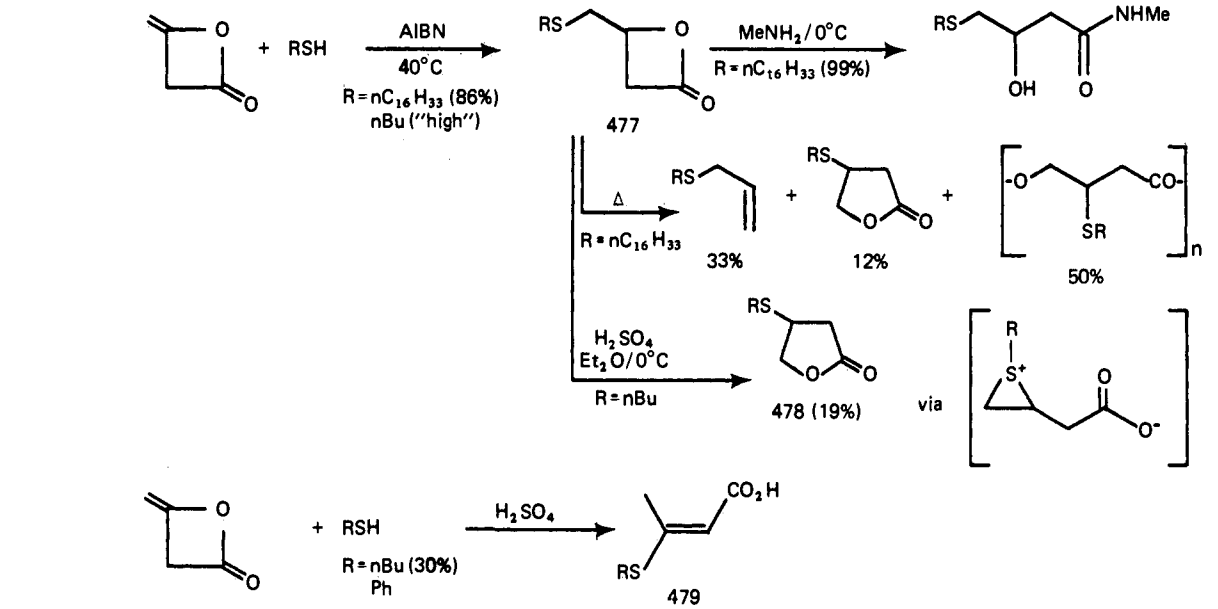
1. Radical Addition Reactions

Although diketene reacts with chlorine to give 4-chloroacetoacetyl chloride, the double bond can be chlorinated with sulfuryl chloride in the presence of a radical initiator to give 4-chloro-4-(chloromethyl)oxetan-2-one (472)[548] (Scheme CCXI). A number of halogenated compounds, including tetrahalomethanes, trichloroacetyl chloride, and trichloroacetonitrile have been added to diketene under radical conditions.[549] The resulting adducts can be ring-opened to provide 4-substituted acetoacetate derivatives.

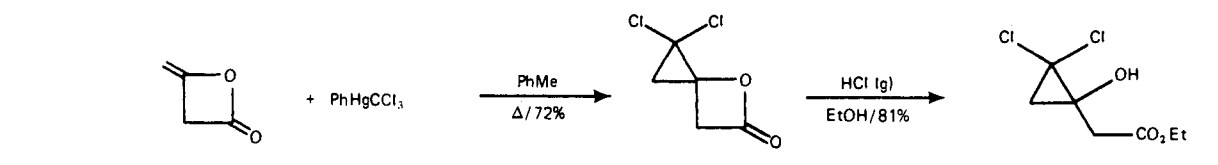
Other compounds which are capable of undergoing homolytic cleavage and addition to olefins also combine with diketene to give 4-substituted oxetanones. For example, diethyl phosphite reacts with diketene via radical cleavage of the phosphorous–hydrogen bond[550] (Scheme CCXII).

Secondary alcohols, such as isopropyl alcohol, react with diketene under radical conditions, and the oxetanones 473 which result have been further converted into conjugated dienoic acids 474 and dihydropyrones 475[551] (Scheme CCXIII).

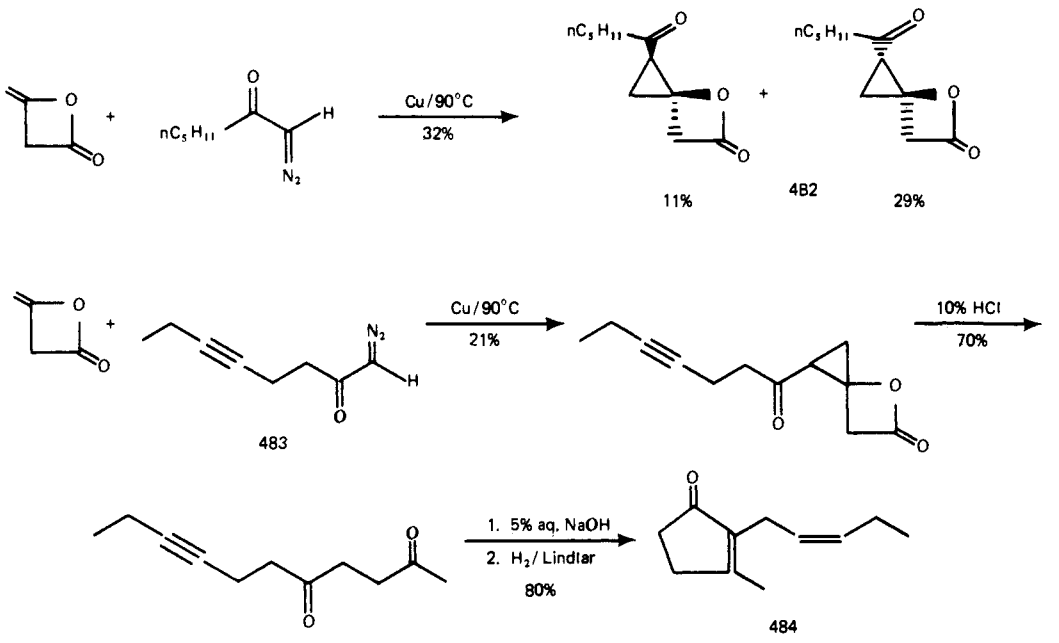
SCHEME CCXV



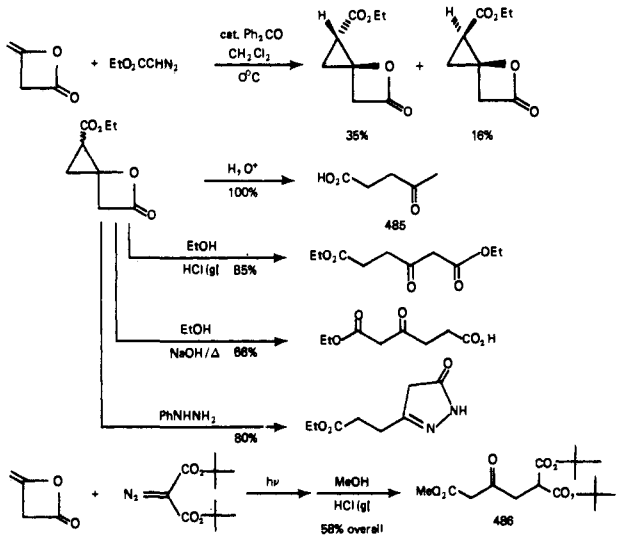
SCHEME CCXVI



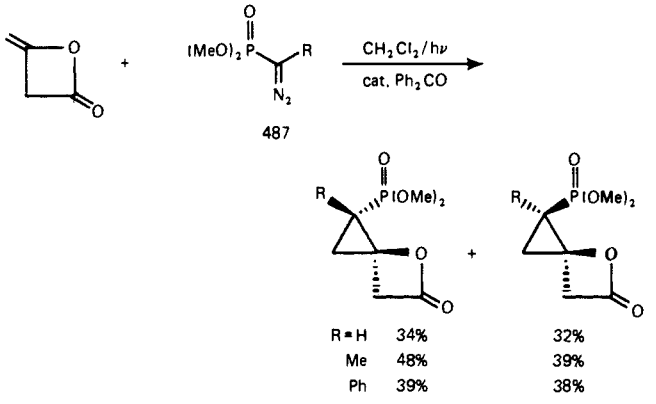
SCHEME CCXVII



SCHEME CCXVIII



SCHEME CCXIX



Sulfur compounds react with the double bond of diketene under both radical and ionic conditions. The highly activated $SClF_5$ reacts spontaneously with diketene, and the resulting adduct **476** can be ring-opened and decarboxylated or dimerized, presumably via an acetoacetyl chloride intermediate[552] (Scheme CCXIV).

Aliphatic thiols undergo an exothermic, radical addition to diketene, and the resulting sulfides (**477**) precipitate from hydrocarbon solvents in high yield[553] (Scheme CCXV). Bis(oxetanones) have been similarly prepared from the reaction of dithiols and diketene.[554] The diketene/thiol adducts **477** have been converted into alkenes, polymers, crotonate esters, and γ-lactones. Pyrolysis of **477** affords a mixture of products that result from either the rearrangement of a thiironium intermediate or from the elimination of CO_2.[553] γ-Lactones, such as **478**, have been prepared by treating adducts **477** with sulfuric acid. The direct reaction of diketene and thiols in sulfuric acid, however, affords β-alkylthiocrotonic acids **479**.[555]

2. Carbene and Nitrene Additions

Carbenes add to the electron-rich double bond of diketene to give spirocyclopropanes.[556] Thus, the addition of dichlorocarbene to diketene affords a bicyclic system (**480**) which, upon treatment with nucleophiles, gives cyclopropylacetate esters such as **481**[557] (Scheme CCXVI).

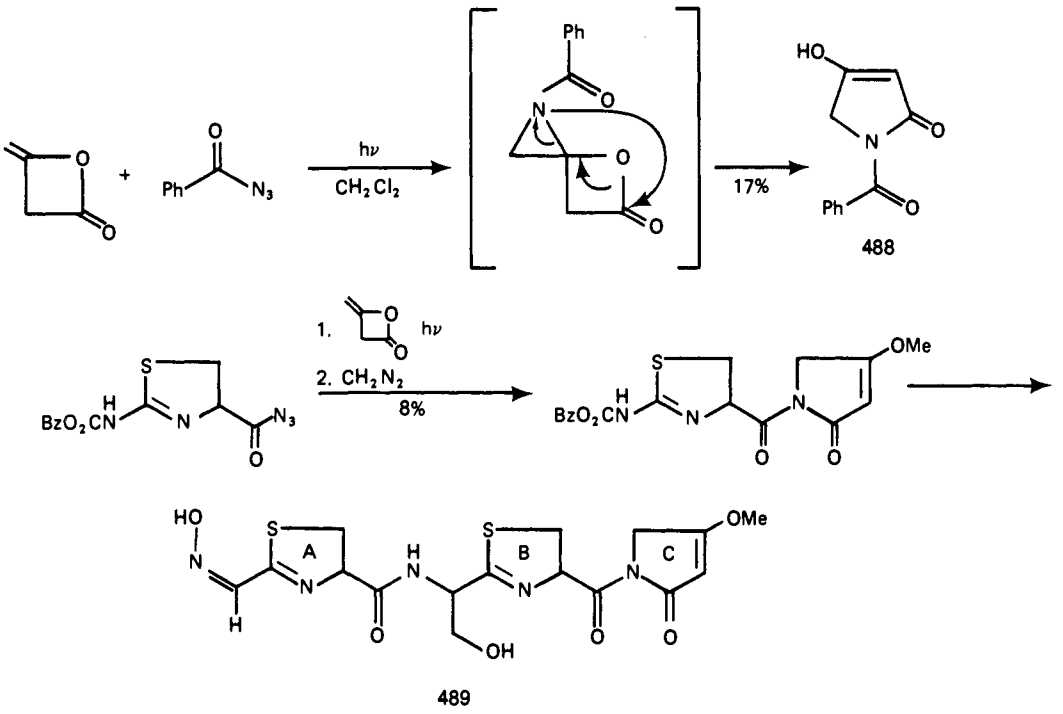
Carbenes generated from pyrolysis or photolysis of diazo compounds also react with diketene to give a mixture of diastereomeric spirocyclopropanes (**482**)[558] (Scheme CCXVII). The reaction of diketene and diazo ketone **483** has been used in yet another preparation of *cis*-jasmone (**484**).[559]

Ethyl diazoacetate reacts with diketene to provide two diastereomeric spirocycles which have been converted into levulinic acid (**485**) and other derivatives[558,560] (Scheme CCXVIII). Di-*tert*-butyl diazomalonate and diketene have been used to prepare the unsymmetrical keto triester **486**.[561]

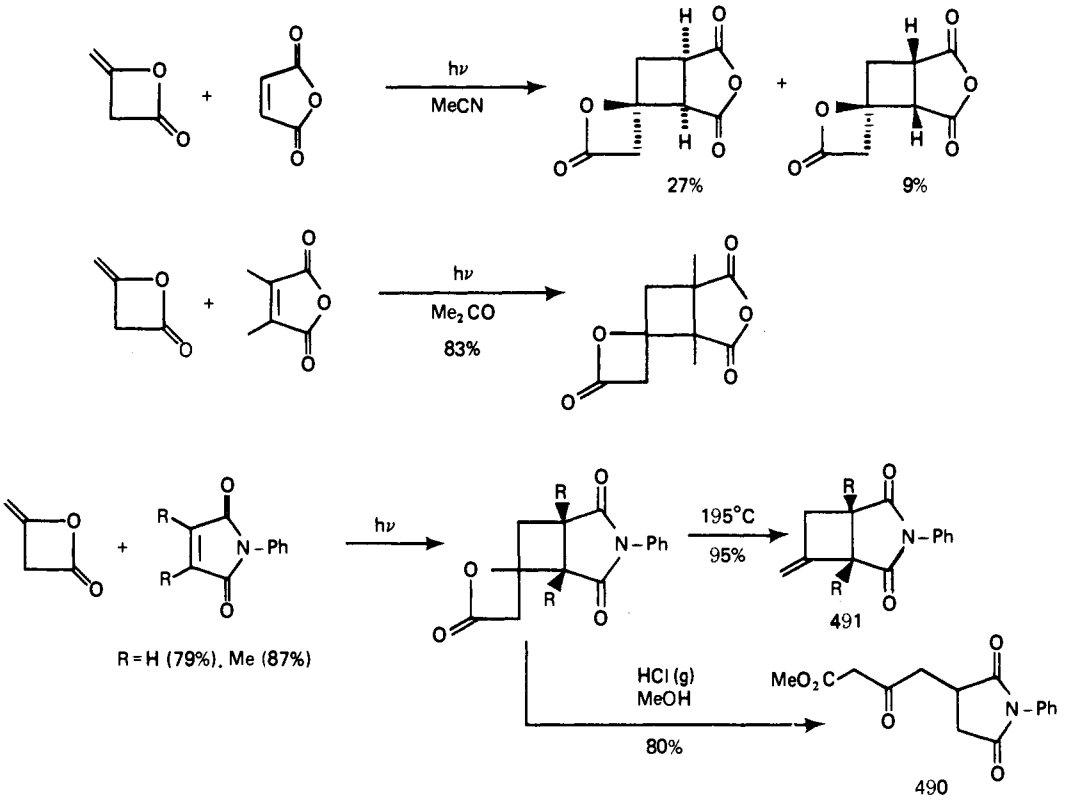
Other diazo compounds, such as the diazotized phosphite ester **487**, react with diketene to provide cyclopropanes[562] (Scheme CCXIX).

Nitrenes generated from acyl azides or from ethyl

SCHEME CCXX



SCHEME CCXXI

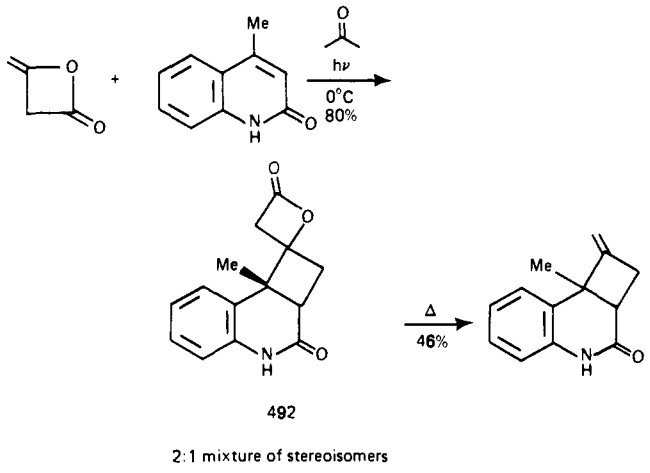


azidoformate also add to the exocyclic double bond of diketene; the spirocyclic intermediates which are produced rapidly rearrange to afford *N*-acyltetramic acids (**488**) in low yield[563] (Scheme CCXX). This preparation of tetramic acids has been used to introduce the pyrrolinone ring (C) during a total synthesis of althiomycin (**489**).[564]

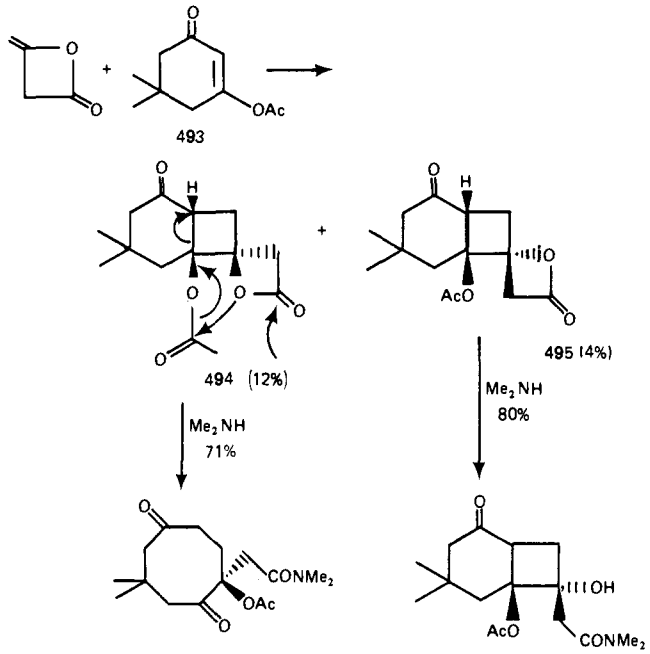
3. *Photochemical [2 + 2] Reactions*

The exocyclic olefin in diketene undergoes photochemical [2 + 2] reactions to give mixtures of diastereomeric spirocyclobutanes (Scheme CCXXI). These [2 + 2] reactions are sensitive to both the substrate and the reaction conditions, with dimethyl maleic anhydride

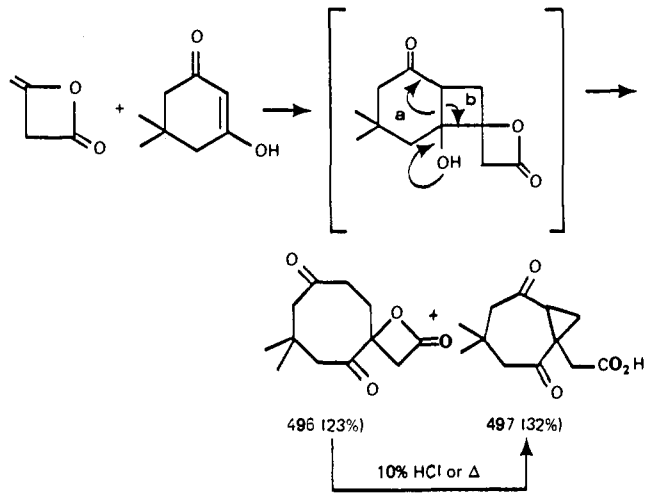
SCHEME CCXXII



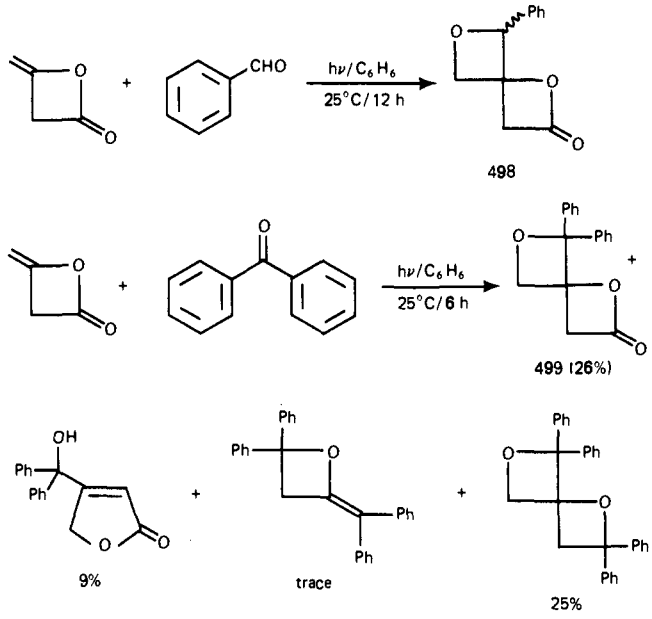
SCHEME CCXXIII



SCHEME CCXXIV



SCHEME CCXXV



(in acetone) providing a much better yield of photoadduct than maleic anhydride (in acetonitrile).[565] *N*-Phenylmaleimides also react with diketene, and the resulting cycloadducts can be ring-opened to give acetoacetates **490** or pyrolyzed to provide methylenecyclobutanes **491**.[566]

Photochemical [2 + 2] reactions have been observed with diketene and uracil,[567] 6-methyluracil,[568] 6-azauracil,[569] isophorone,[570] 4-methoxy-1-methyl-2-pyridone,[571] and a series of 4-substituted-2-quinolones (c.f. **492**)[571] (Scheme CCXXII).

In the photochemical reaction of dimedone acetate (**493**) with diketene, the diastereomeric [2 + 2] adducts **494** and **495** were isolated; the absolute stereochemistry was assigned on the basis of subsequent aminolysis experiments[572] (Scheme CCXXIII).

The initially derived products from the photochemical [2 + 2] reaction of dimedone with diketene were not obtained, but instead the ring-expanded products **496** and **497** were isolated[570] (Scheme CCXXIV).

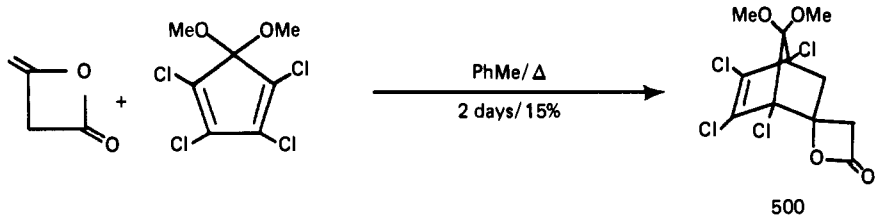
Carbonyl compounds also react with diketene via photochemical [2 + 2] reactions. The primary adduct **498** is isolated when benzaldehyde is reacted with diketene (Scheme CCXXV). The use of benzophenone in the above reaction results in the formation of a mixture of products, all arising from the initially formed photocycloadduct **499**.[573]

4. *Other Cycloaddition Reactions*

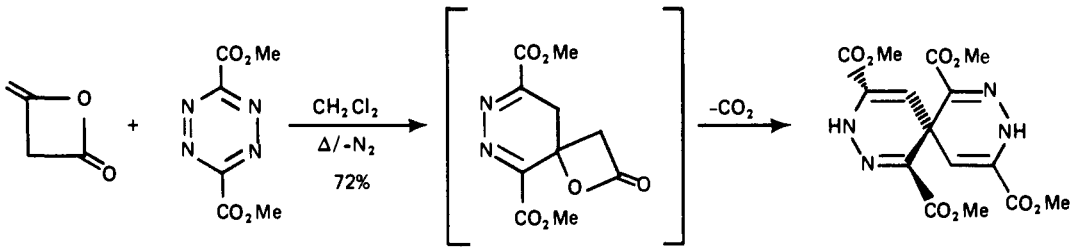
The double bond of diketene participates in thermal [4 + 2] cycloaddition (Diels–Alder) reactions. For example, diketene acts as an electron-rich dienophile when reacted with dimethoxytetrachlorocyclopentadiene and provides spirocyclic adduct **500** in low yield[574] (Scheme CCXXVI). In a Diels–Alder reaction with 3,6-bis(carbomethoxy)tetrazine (**501**), however, diketene acts as an allene equivalent because the primary adduct **502** decarboxylates spontaneously.[575]

In the reaction of diketene with nitrile oxide **503**, the primary cycloadduct rapidly decarboxylates and the decarboxylated product reacts further (Scheme CCXXVII); diketene thus becomes an allene equivalent

SCHEME CCXXVI

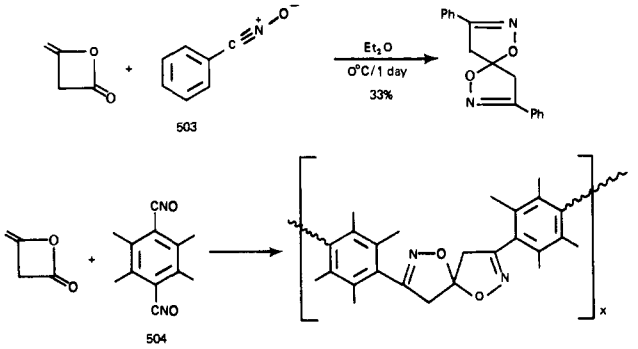


500



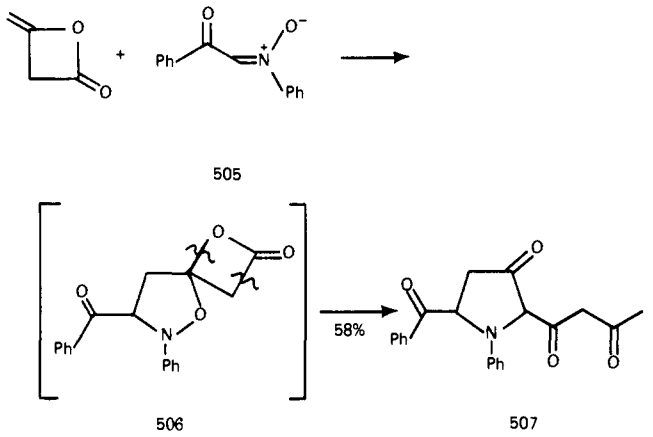
501 502

SCHEME CCXXVII



503 504

SCHEME CCXXVIII



505 506 507

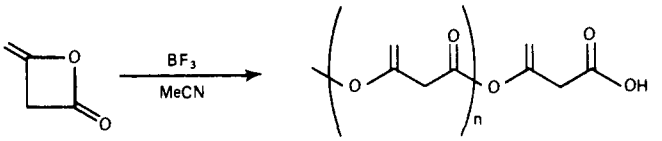
in this reaction.[576] Bis nitrile oxides, such as **504**, combine with diketene to form high molecular weight polymers.[577]

Diketene combines with nitrone **505** to form the intermediate cycloadduct **506**, which loses CO_2, rearranges, and is then acetoacetylated to afford pyrrolidinone **507**[578] (Scheme CCXXVIII).

C. Polymerization of Diketene

Diketene can be polymerized with $HgCl_2$[579] or with an ion-exchange resin[193] to afford a low molecular weight polymer (**508**, $M \sim 1630$) containing unconjugated methylene groups in the monomer unit (Scheme CCXXIX). Crystalline diketene polymers have also been prepared by using BF_3[580] or metal hydroxides as the catalysts.[581] Degradation of the above polymers in acidic methanol yields methyl acetoacetate; this decomposition provides evidence for enol ester structures. Diketene can be polymerized with γ radiation[582] in a polymerization which has been shown to proceed via a cationic intermediate.[583] Metal chelate catalysts also convert diketene into liquid polymers.[584]

SCHEME CCXXIX



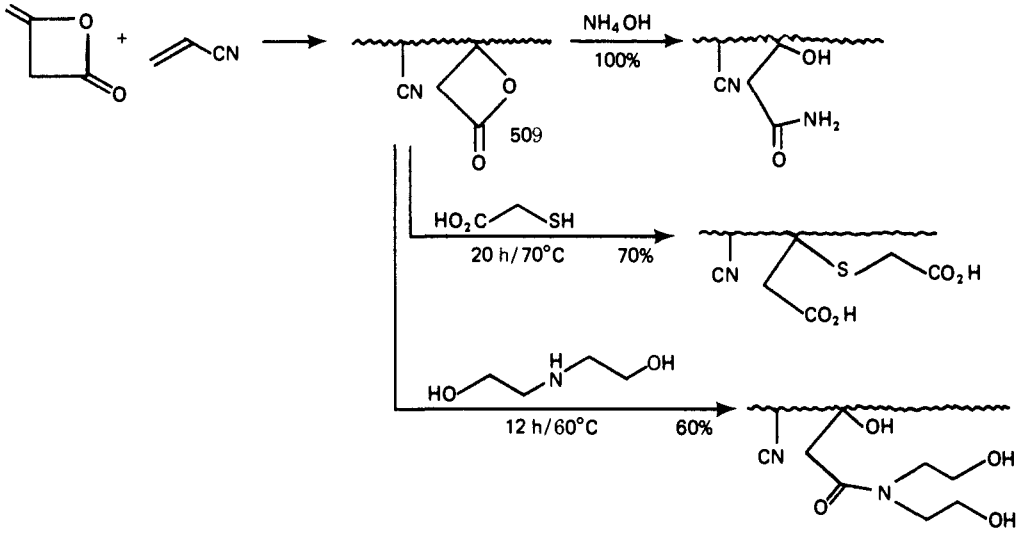
508

Diketene can be copolymerized under free radical conditions to afford a polymer which contains a β-lactone ring in the monomer unit; diketene readily forms copolymers with other vinyl monomers such as vinyl acetate, vinyl chloride, vinylidene chloride, and acrylonitrile.[585] Polymers containing up to 20 mol % diketene were found to be suitable for use as fibers.[586] The β-lactone rings in the diketene/acrylonitrile copolymer **509** have been reacted with nucleophiles to provide more elaborately functionalized polymers[586,587] (Scheme CCXXX). Several of these functionalized diketene copolymers are claimed to be useful in films and fibers,[588] pressure-sensitive adhesives,[589] and metal extraction.[590] A 1:1 poly(vinylidene cyanide)-*co*-diketene polymer has been ring opened with a variety of nucleophiles to produce dye-receptive copolymers.[591]

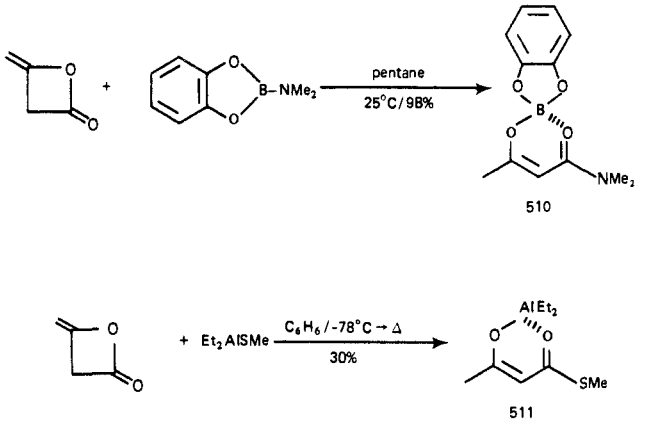
D. Reactions with Organometallic Reagents and Related Compounds

Acetoacetate derivatives chelate with metal ions, and these chelates have often been used in the purification

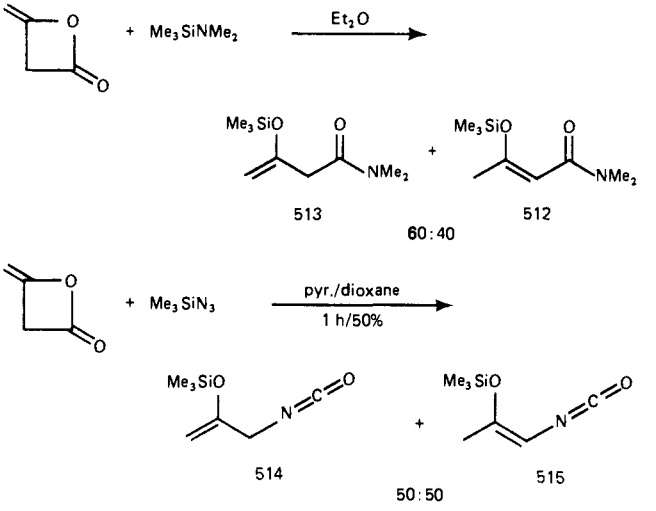
SCHEME CCXXX



SCHEME CCXXXI



SCHEME CCXXXII



of acetoacetates. Diketene reacts with organoboron, organoaluminum, and organotin compounds to afford acetoacetate complexes such as **510** and **511**[592] (Scheme CCXXXI).

When diketene is reacted with (dimethylamino)trimethylsilane a mixture of the conjugated (**512**) and the unconjugated (**513**) enol ethers is isolated[593] (Scheme CCXXXII). No effort was made to optimize formation of the unconjugated product, which could be a useful synthetic intermediate. In a related reaction, trimethylsilyl azide reacted exothermically with diketene; a mixture of isocyanates **514** and **515** was isolated by distillation.[594]

Diketene "inserts" into the tin–nitrogen bond of *N*-(trimethylstannyl)benzophenone imine (**516**) to afford an unconjugated stannyl enol ether which can be cyclized into a piperidine-2,4-dione[595] (Scheme CCXXXIII).

Silylated phosphines and diketene combine to afford the unconjugated enol ethers **517**, which can either be partially isomerized or hydrolyzed to give phosphino esters **518**[596] (Scheme CCXXXIV). Diketene is reported to react with dimethyl *O*-trimethylsilyl phosphite to provide the orthoester **519**.[597]

Diketene reacts with palladium(II) compounds and water to form π-allyl complexes of acetoacetic acid (**520**);[598] the use of alcoholic solvents affords complexes of acetoacetate esters[96] (Scheme CCXXXV). The addition of pyridine to these latter complexes causes rearrangement of the π-allyl complex to the 4-σ complex (**521**).[599] These 4-σ complexes (**521**) have been carbonylated to afford esters of acetonedicarboxylic acid (**522**).[600] A recent patent describes the direct conversion of diketene, carbon monoxide, and methanol into dimethyl acetonedicarboxylate in the presence of methyl nitrite and palladium(II) chloride.[601]

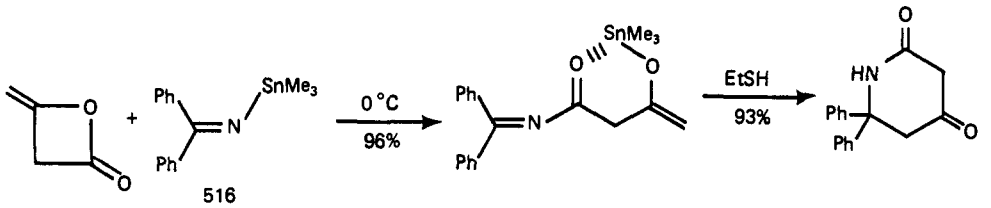
Treatment of mercury(II) compounds with diketene gives acetoacetates mercurated in the 2-position; these intermediates (**523**) have been used in the preparation of methyl 2-bromoacetoacetate[602] (Scheme CCXXXVI).

Diketene reacts with the cyclopentadienyldicarbonylmanganese–THF complex to afford the η^2-allene complex[603] and with an osmium cluster compound to afford the η^2-allene cluster complex and carbon dioxide[604] (Scheme CCXXXVII). Reaction of diketene with a nickel(0) compound yielded carbon dioxide and a polymer derived from allene.[605]

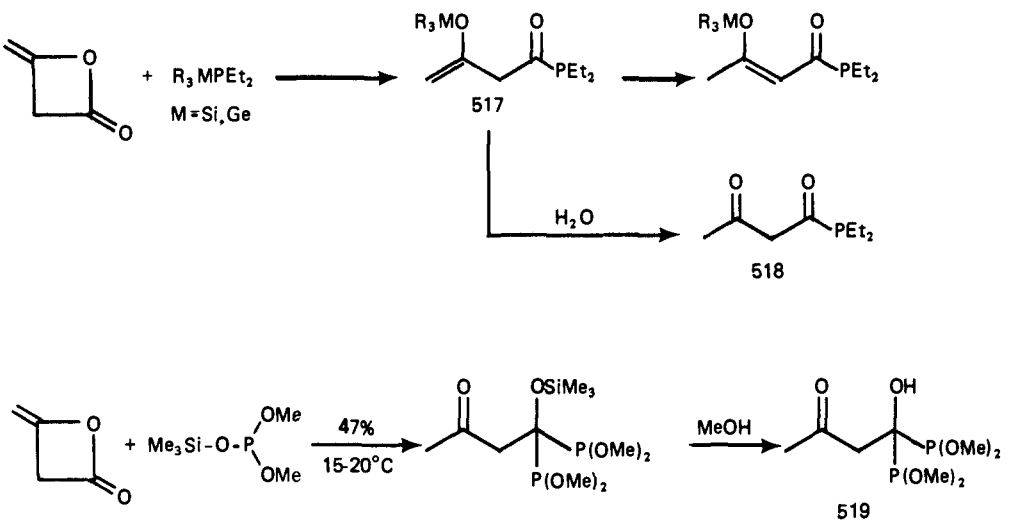
Diketene has been successfully carbonylated, albeit with low conversion, to provide methyl succinic anhydride (**524**)[606] (Scheme CCXXXVIII).

Early research into the reaction of diketene with Grignard reagents was disappointing. Methylmagnesium iodide reacted with diketene to give traces

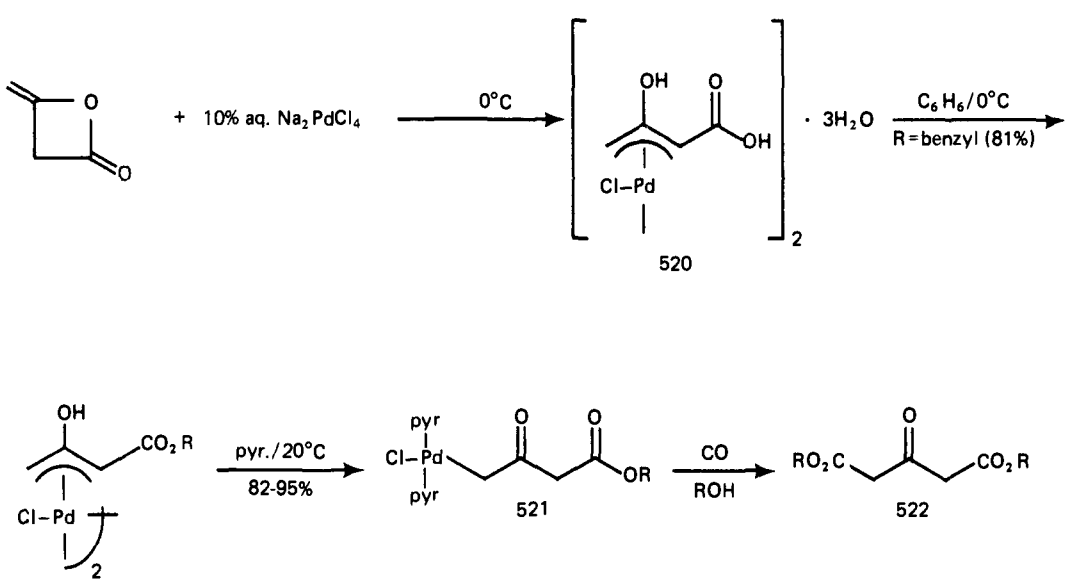
SCHEME CCXXXIII



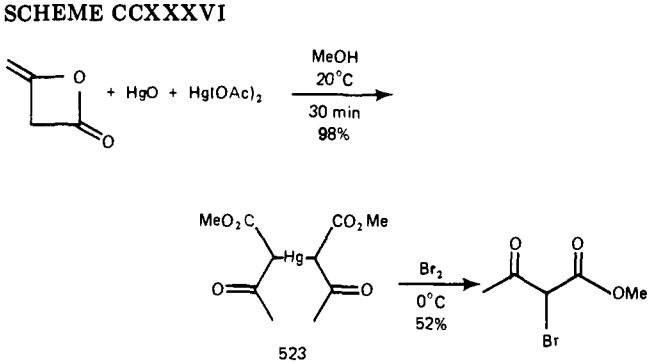
SCHEME CCXXXIV



SCHEME CCXXXV



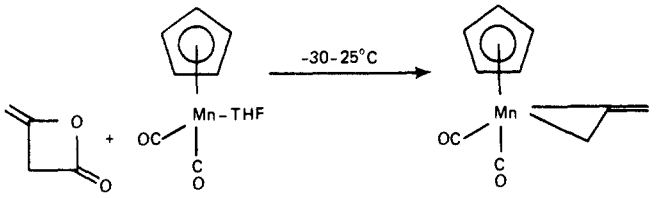
SCHEME CCXXXVI



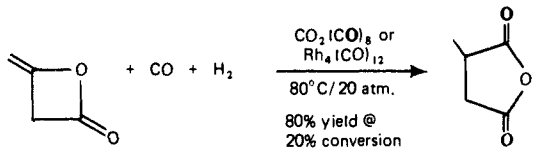
of mesityl oxide, presumably formed from diacetone alcohol, and large amounts of dehydroacetic acid.[11b,14] A thorough study of the diketene/Grignard reaction showed that diketene reacts with phenylmagnesium bromide to afford acetophenone and diphenylmethylcarbinol.[287]

In the presence of a nickel(II) catalyst, (trimethylsilyl)magnesium chloride reacts with diketene at the olefinic carbon–oxygen bond to give 3-methylene-4-(trimethylsilyl)butyric acid (**525**)[607] (Scheme CCXXXIX). Palladium, cobalt, and copper catalysts are less effective. The product of this Grignard reaction has been converted into dihydropyrones **526**[608] and has

SCHEME CCXXXVII



SCHEME CCXXXVIII



524

been alkylated to afford an intermediate **527** which has been used to prepare (±)-trixagol (**528**).[609]

Other Grignard reagents add to diketene in the presence of cobalt(II) iodide. A variety of 3-methylene carboxylic acids **529** have been prepared from Grignards which were derived from both saturated and unsaturated primary halides[610] (Scheme CCXL); secondary and tertiary Grignards provided greatly reduced yields. The addition of a Grignard reagent to diketene has also been used in the synthesis of several terpenoids and of the *Cecropia juvenile* hormone.[610] With nickel or palladium catalysts, organozinc and organoaluminum compounds add to diketene in a fashion similar to that of Grignard reagents.[611]

VII. Conclusion

A general summary of diketene chemistry might be that the fundamental reactions of diketene (hydrogenation, halogenation, acetoacetylation) are well understood, but that many other diketene reactions are not well developed. Because of economic interests, excellent diketene-based routes to diazinon and aminothiazoleacetic acid have been developed; thus, the potential of diketene as an intermediate for the preparation of heterocycles is clearly demonstrated. Hopefully, this review will make some of the unexplored areas of diketene chemistry more apparent, will encourage further development of the underexplored areas, and will stimulate new ideas for diketene chemistry.

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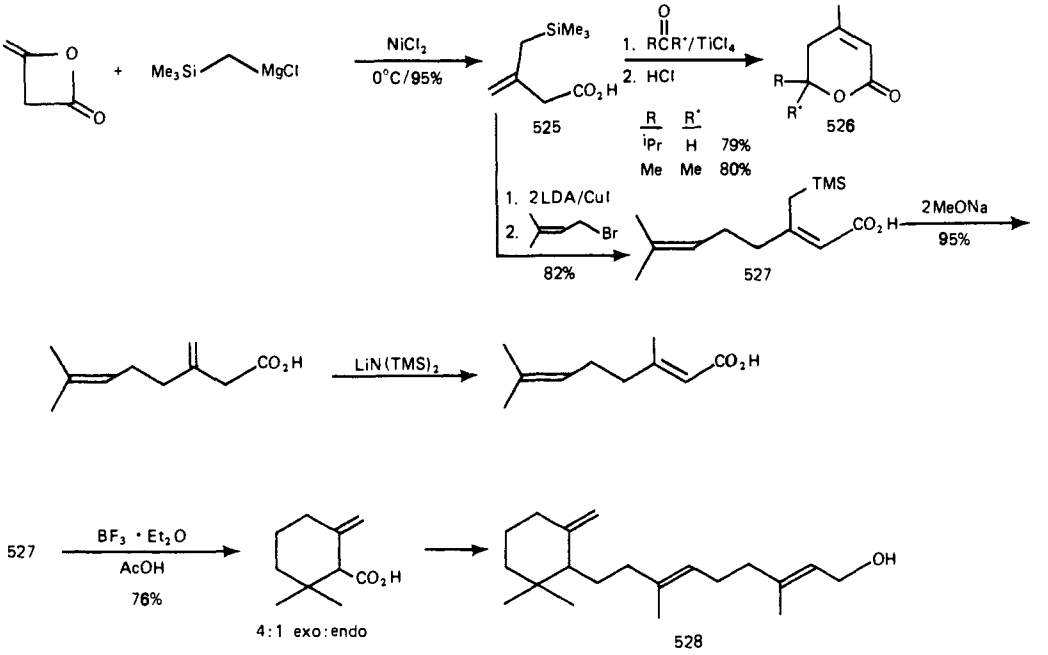
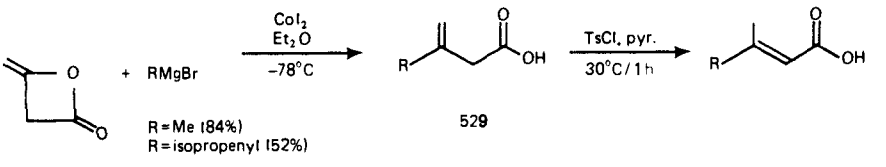
Addendum

The slow decomposition of diketene in the presence of acetic acid has been studied.[612] Pyrolysis of O-acetoacetylated hydroxamic acids affords isocyanates in good yield.[613] An enantioselective synthesis of

SCHEME CCXXXIX



SCHEME CCXL



(+)-geissochizine (345) has been developed.[614] Several 4-hydroxy-2-pyrones and 4-hydroxycoumarins have been acetoacetylated at C-3 with diketene under basic conditions.[615] The application of diketene in heterocyclic synthesis continues: the scope of the intramolecular condensation of acetoacetanilides with nitro groups (Scheme CLIV) has been increased,[616] and a rhodium-catalyzed carbenoid insertion has been used to prepare 4-acetyl-1,2-diazetidin-3-ones from α-diazoacetoacetohydrazides.[617] Thiadiazines were prepared from diketene and *S,S*-dialkylsulfur diimides,[618] and some 2-substituted pyrimidines and 3-acetyl-2-aminopyridines were prepared from diketene and 4-amino-1-azabutadienes.[619]

Registry No. Diketene, 674-82-8.

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