INTRAMOLECULAR [2+2] CYCLOADDITIONS OF KETENES

DISSERTATION

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Fulfillment of the Requirements

For the Degree of

DOCTOR OF PHILOSOPHY

By

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The objective of this study was to explore intramolecular ketene cycloadditions with the anticipated results of developing new synthetic methodology for the synthesis of polycyclic compounds difficult to obtain by other procedures.

(o-Alkenylphenoxy)ketenes were initially selected for this study because these ketenes provided a favorable proximity for the intramolecular [2+2] cycloaddition reactions. The difunctional precursors, (o-alkenylphenoxy)-acetic acids, were readily prepared from o-alkenylphenols and α-halocarboxylic acids and were converted to the corresponding acid chlorides by reaction with oxalyl chloride.

The acid chlorides were dehydrochlorinated to the corresponding (o-alkenylphenoxy)ketenes by treatment with triethylamine. The ketenes undergo a facile intramolecular [2+2] cycloaddition to give polycyclic cyclobutanones. The (o-vinylphenoxy)ketenes are clearly more reactive than the (o-allylphenoxy)ketenes and provide much better yields of the cycloaddition products because of electronic effects in the transition state in the cycloaddition process.

The intramolecular [2+2] cycloadditions of keteniminium salts were included in this study as a more electrophilic alternative to ketenes that will react with less nucleophilic

carbon-carbon double bonds. However, the use of keteniminium salts instead of ketenes in intramolecular cycloadditions does have some limitations.

The synthesis of benzofurans via the intramolecular [2+2] cycloadditions of (o-acylphenoxy)ketenes was accomplished. The initially formed β-lactone cycloaddition products spontaneously underwent decarboxylation to the benzofurans. The aromaticity of the benzofurans is apparently a very strong driving force for the cycloaddition.

During the course of this study, two new synthetic methods were discovered which in many instances represent a significant improvement over existing methods. The Wittig Reactions of ketoacids without protecting the carboxyl groups provide a reliable source of the precursor unsaturated acids needed for intramolecular ketene-olefin cycloadditions. Also, the one-pot preparation of intramolecular ketene cycloaddition products from the carboxylic acid via the tosylate represents a new synthetic method. This procedure eliminates the acid halide preparation, isolation and purification step, thereby significantly simplifying the synthesis.

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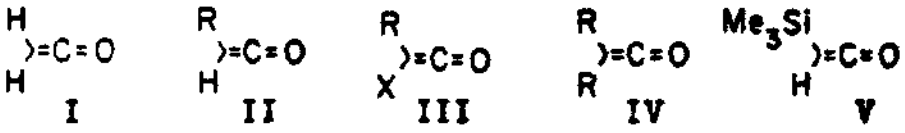
INTRODUCTION

Ketenes are highly reactive electrophilic organic compounds which contain an olefinic and a carbonyl group in a cumulative linkage. The simplest member of this family of compounds is the unsubstituted ketene (I).

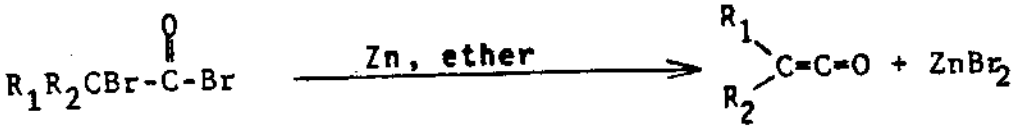


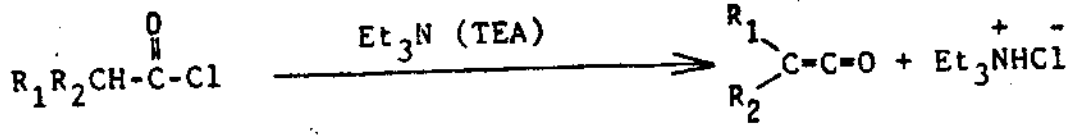
I II III IV V

Most aldoketenes (II), monosubstituted ketenes, and halogenated ketenes (III, defined as ketenes with one or two halogen atoms directly bonded to the ketene functionality) are not stable at room temperature and are usually trapped <u>in situ</u> with suitable ketenophiles (1, 2, 3, 4, 5, 6). Some ketoketenes (IV), disubstituted ketenes, such as diphenylketene, diethylketene, etc, are relatively stable and are isolable at room temperature (7, 8, 9). Trimethylsilylketene (V) is, however, an exception in that it is a stable isolable aldoketene that can be stored neat for several weeks under refrigeration (10).

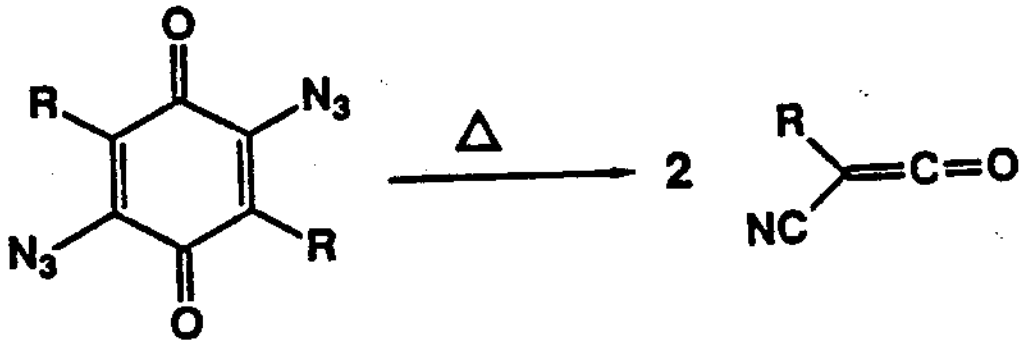
The first reported synthesis of a ketene was in 1905 when Staudinger reported the synthesis of the isolable diphenylketene (11). Staudinger and coworkers studied many reactions of a number of substituted ketenes (12, 13, 14, 15, 16, 17) and published in 1912 the first review of the chemistry of ketenes (18).

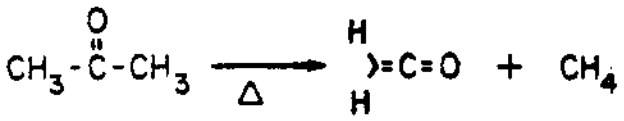
There are many methods which have been reported for the preparation of ketenes but the most common and synthetically useful are the dehydrohalogenation of appropriately substituted acid halides with a tertiary amine such as triethylamine and dehalogenation of α-haloacid halides with activated zinc as illustrated (1, 2, 3, 4, 5, 19, 20, 21, 22).

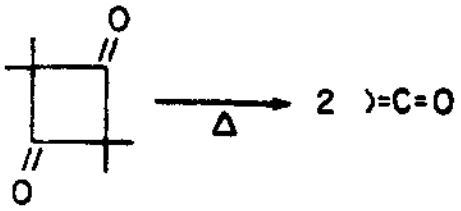


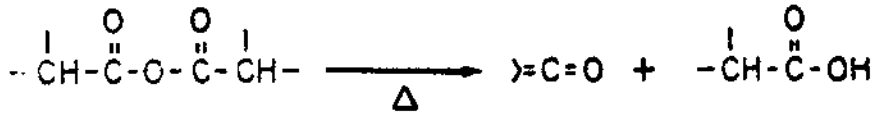


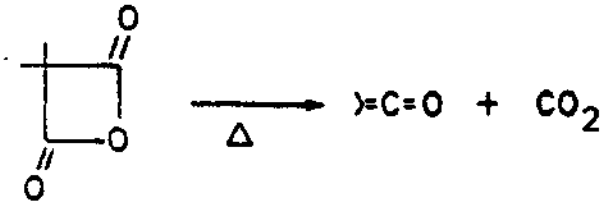
The pyrolysis of appropriate compounds may be used for the preparation of a few ketenes, particularly cyanoketenes (23, 24) and ketenes of low molecular weight (7, 25, 26, 27, 28).

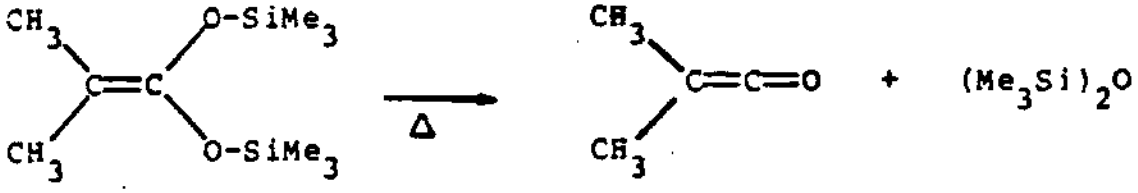




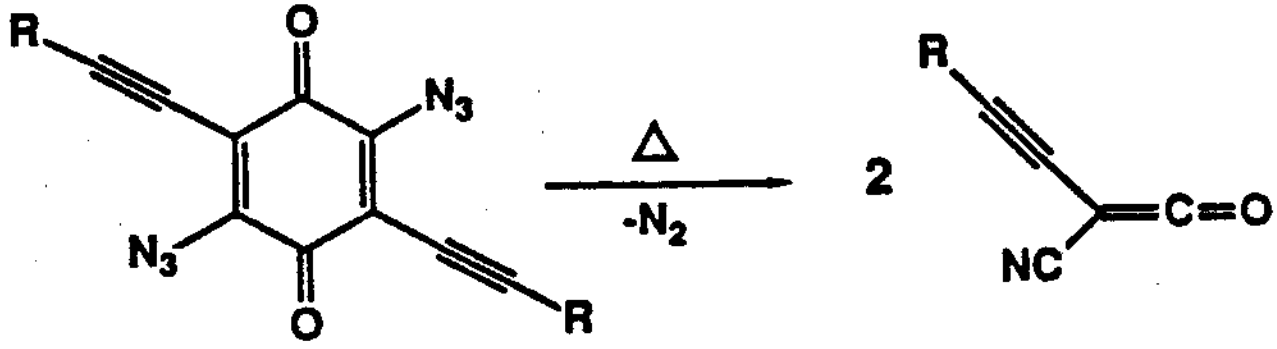


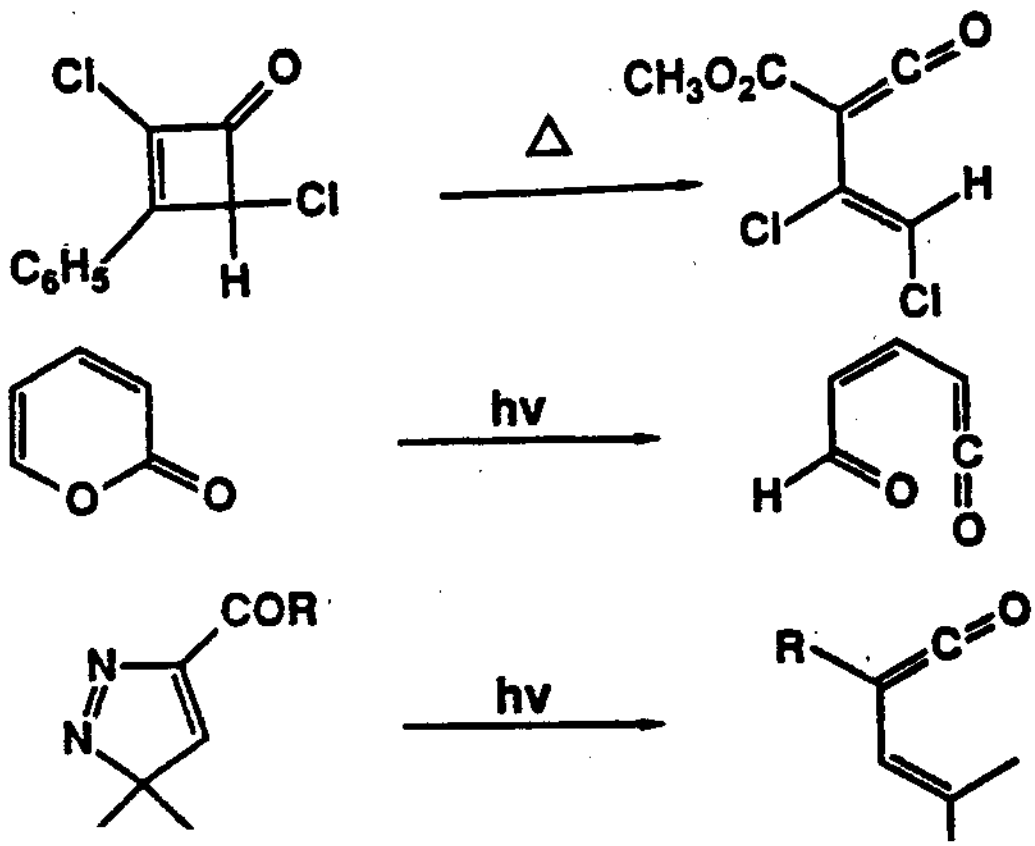






Recently, several lesser known ketenes such as alkynylketenes and vinylketenes have been prepared by taking advantage of the thermo- or photochemical properties of some specially synthesized ketene precursors (24, 29, 30).



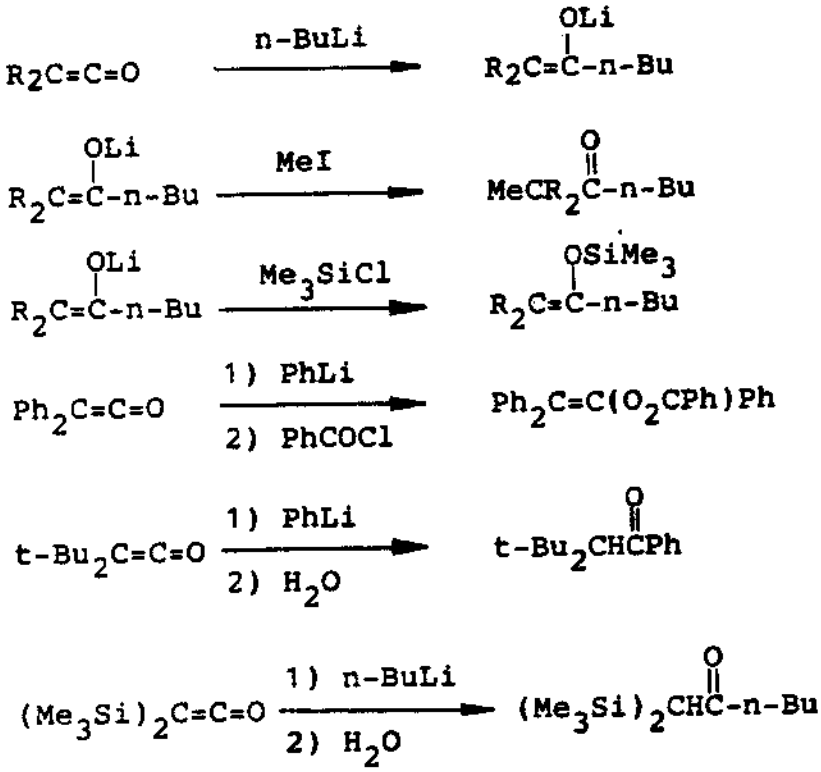


There are essentially four general reactions which ketenes undergo: cycloaddition, nucleophilic addition, dimerization and polymerization. These latter two reactions are usually considered undesirable and efforts are made to minimize dimerization and polymerization. The nucleophilic addition of amines, alcohols, acids, water, etc., to ketenes to yield acylation products (31) has not received the attention that cycloaddition reactions have in the literature.

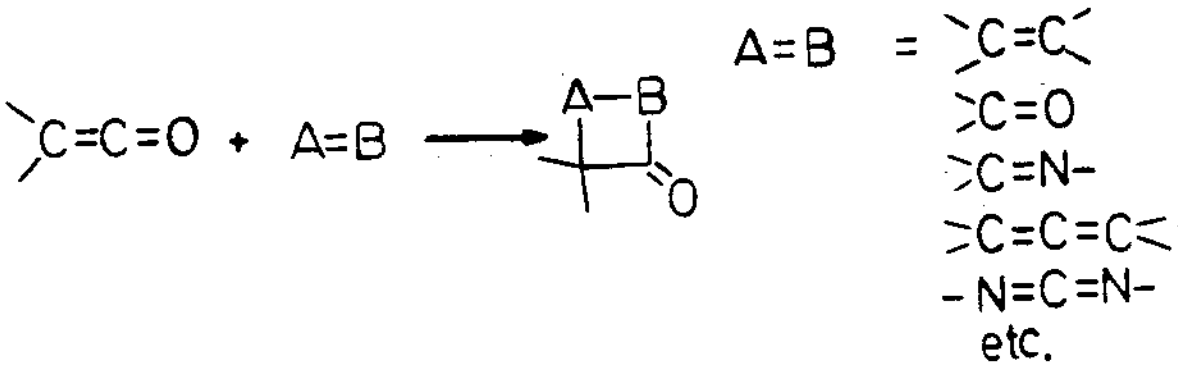
$$)=C=O + HNu \longrightarrow -\overset{|}{C}H-\overset{O}{\overset{\|}{C}}-Nu$$

However, there has recently been considerable activity in the study of addition reactions of ketenes other than cyclo-

additions that has included both the synthetic and mechanistic aspects of these processes. The generation, alkylation and silylation of directed enolates formed by reaction of ketenes and organolithium reagents illustrates this new interest (32).

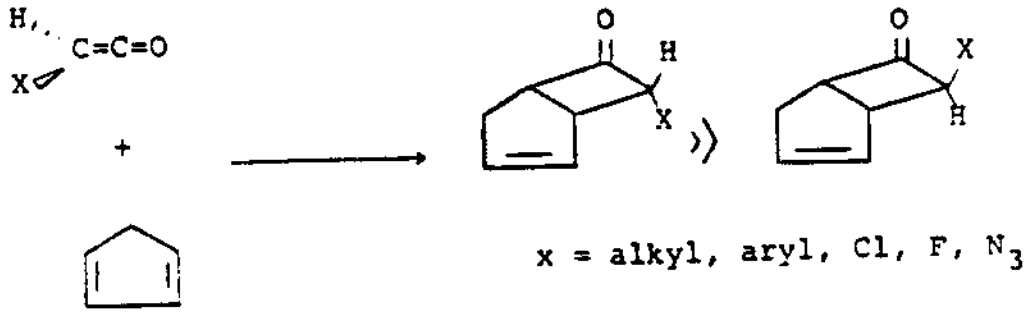


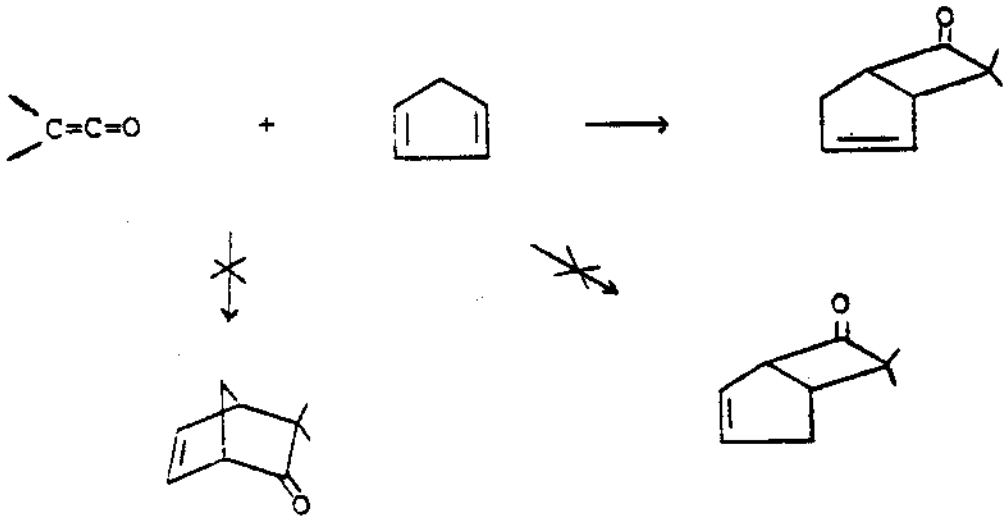
Clearly, the most synthetically useful ketene reaction is the [2+2] cycloaddition with unsaturated compounds to form compounds with four-membered rings as illustrated. This reac-



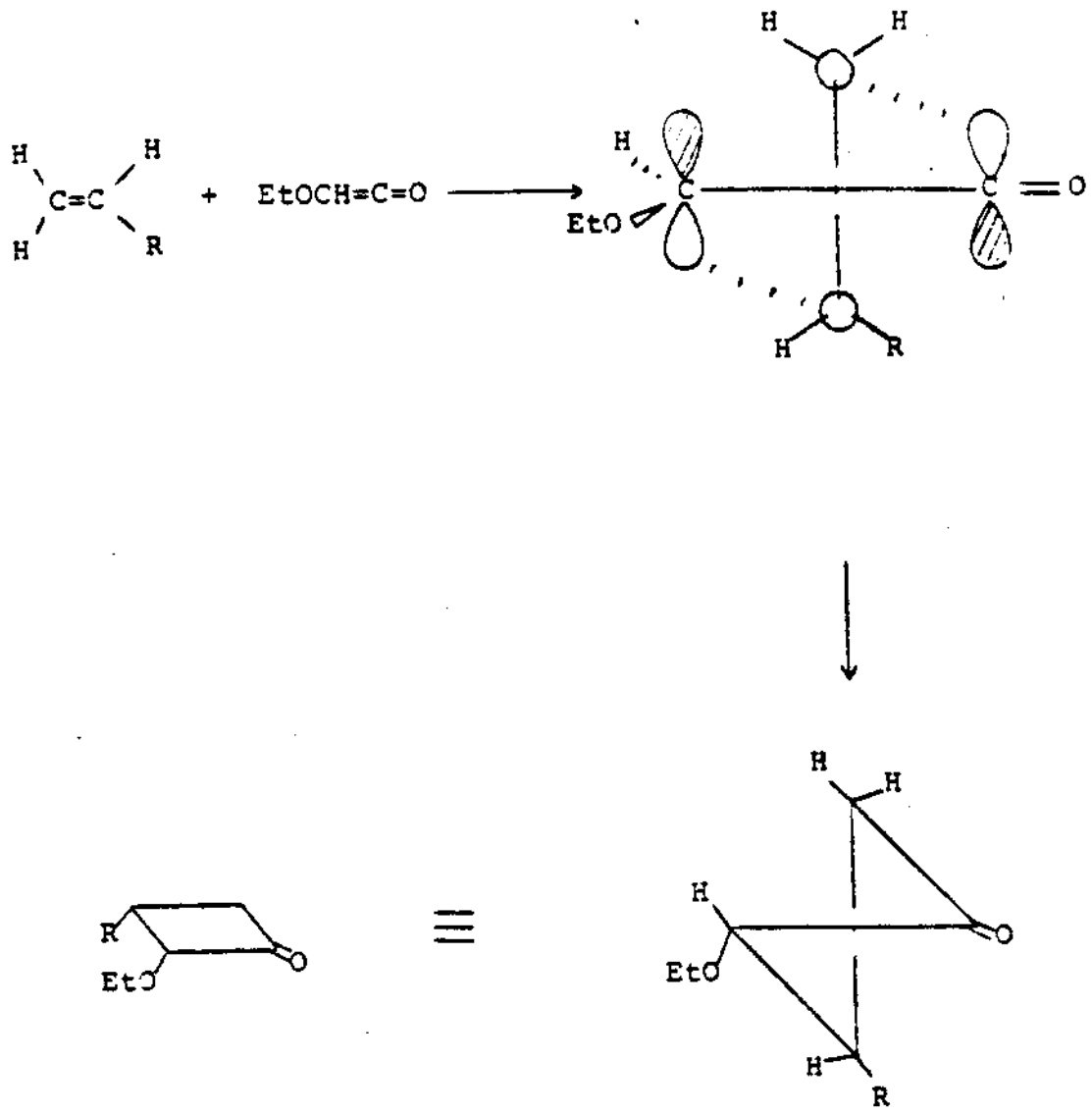
tion constitutes one of the few routes to synthetically versatile four-membered rings. The regiospecificity of this reaction has made it particularly useful in the synthesis of polycyclic natural products (33, 34, 35, 36). The developments in the past few years involving halogenated ketenes have greatly widened the scope and utility of this important synthetic reactions (37, 38, 39, 40, 41). In this [2+2] cycloaddition reaction, ketenes function as electrophiles, while the unsaturated ketenophiles are usually electron-rich nucleophilic reagents. The most electron-deficient atom of the ketene functionality is the sp-hybridized carbon of the carbonyl group (19, 20, 21, 22). The unsaturated ketenophile may be composed of carbon-carbon, carbon-oxygen, carbon-nitrogen, or other unsaturated linkages.

The [2+2] cycloaddition of a ketene and an olefin yield a cyclobutanone. The cyclobutanone arises from a [2+2] cycloaddition process exclusively, even with conjugated dienes. There are many [2+2] ketene cycloadditions with symmetrical and unsymmetrical olefins to give stereo- and regiospecific products (42, 43, 44, 45, 46, 47, 48).





These results are consistent with a concerted mechanism. A lot of evidence including negative activation entropy (49), negligible solvent effects on rate (49), and observed secondary isotope effects (50, 51) has been reported in the literature and has suggested a concerted mechanism which follows a thermal $[\pi^2_s + \pi^2_a]$ pathway for this cycloaddition reaction. The conservation of orbital symmetry dictates that there must be an orthogonal approach in which the π system of the ketene acts in an antarafacial manner and the π system of the olefin, in a suprafacial manner. Thus, the regiospecificity can be explained by the fact that the largest coefficient carbon



of the HOMO of the olefin overlaps with the largest coefficient carbon of the LUMO of the ketene. The transition state resulting from the orthogonal approach of the reacting species, however, accounts for the observed stereochemical results. The least hindered approach of the reacting species

leads to the most hindered product.

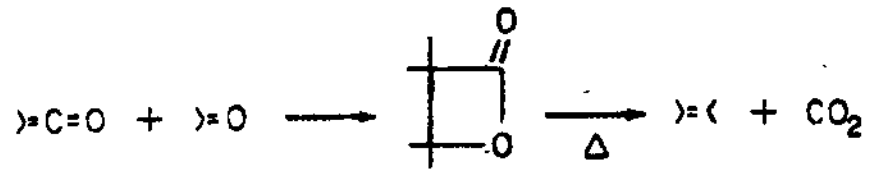
A general order of reactivity for variously substituted ketenes in cycloaddition reactions with olefinic compounds is as follows (5) :

$$Cl_2C{=}C{=}O \;>\; Ph_2C{=}C{=}O \;>\; Me_2C{=}C{=}O \;>\; H_2C{=}C{=}O.$$

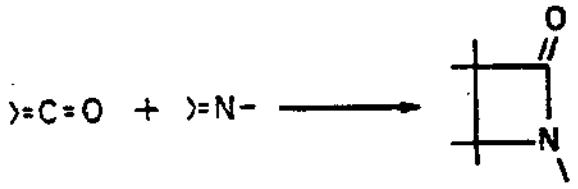
Conversely, the reactivity of olefins in these reactions parallels their nucleophilicities and the energies of their HOMO's.

As the ketenophiles become more electron-rich, i.e., the cation-stabilizing ability of the ketenophile substituents is increased, the typical concerted $[\pi 2_s + \pi 2_a]$ process no longer occurs. Instead, a stepwise mechanism involving a dipolar intermediate becomes operative. Tetraalkoxyethylenes, ketene acetals, imines and carbodiimides are examples of electron-rich ketenophiles which undergo cycloaddition via a dipolar intermediate. In some instances, the intermediates have been trapped (52, 53, 54, 55). Likewise, the increase in anion-stabilizing ability of the ketene substituents favors the stepwise pathway as demonstrated by the studies of England and Krespan (56).

Ketenes will undergo [2+2] cycloaddition reactions with carbonyl compounds under the appropriate conditions to yield 2-oxetanones (β-lactones). In many instances the 2-oxetanones are quite susceptible to decarboxylation thus providing an olefin synthesis (57, 58, 59, 60).



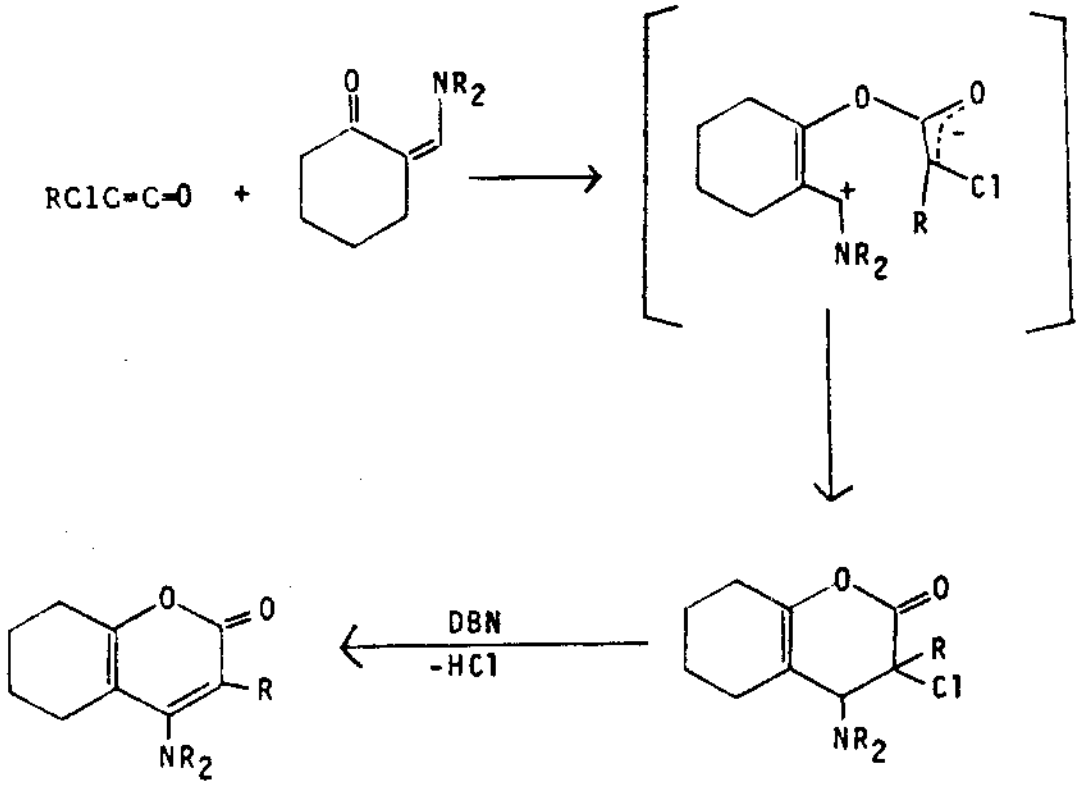
The cycloaddition reactions of ketenes with imines yields 2-azetidinones (β-lactams) (61, 62, 63).



Despite the preferred tendency of ketenes to undergo [2+2] cycloaddition reaction with dienes, ketenes do undergo [4+2] cycloaddition with certain activated vinyl ketones (64, 65, 66, 67) and α,β-unsaturated imines (68, 69, 70). The application of [4+2] cycloaddition reaction of ketenes has been recently reported in the literature to be extremely useful for the syntheses of a wide variety of cyclic natural products (71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83).

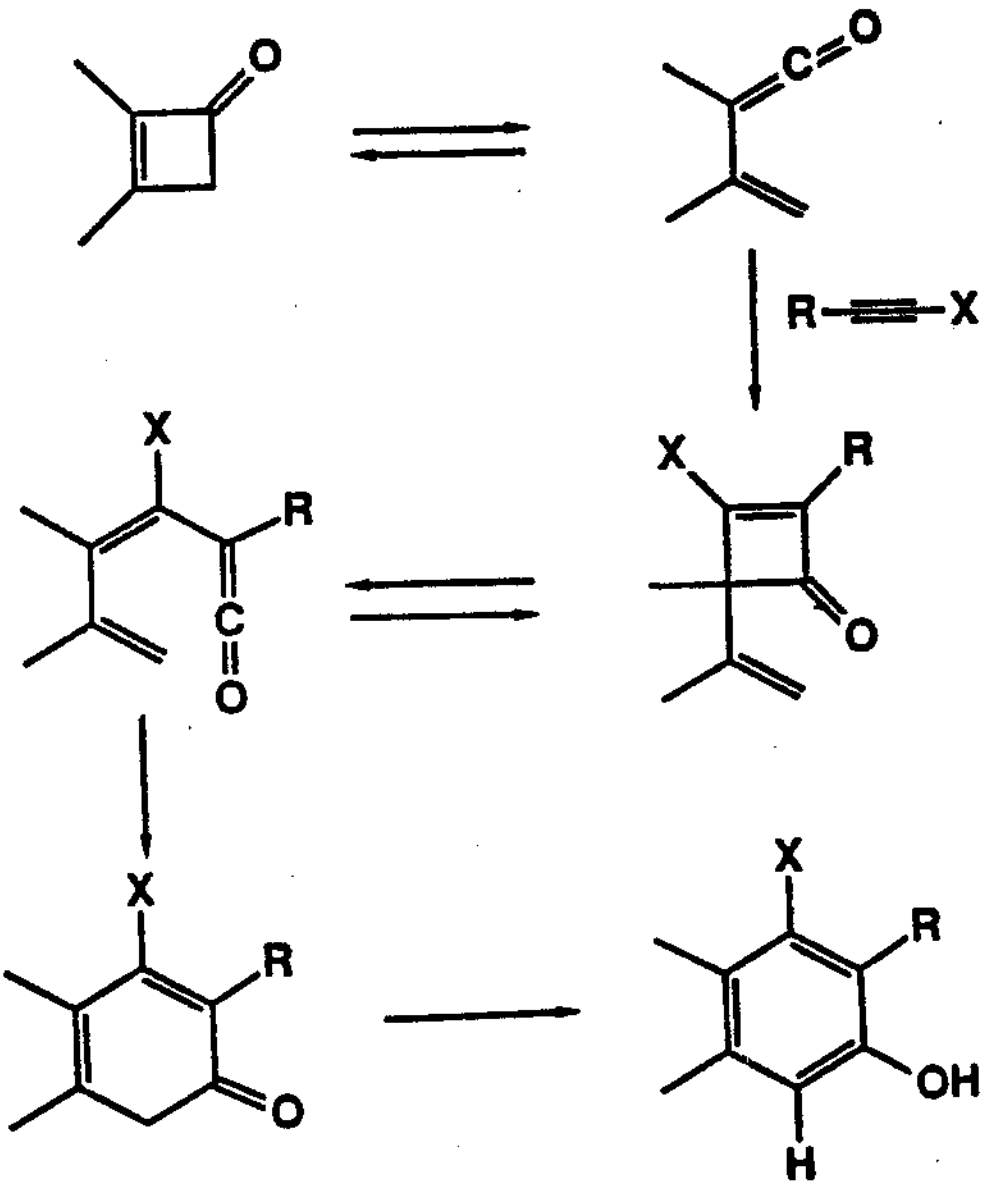
The [4+2] cycloaddition reactions of ketenes have been rationalized in terms of the stepwise mechanism (36, 64, 65, 67, 71); the initial nucleophilic attack of the ketenophile

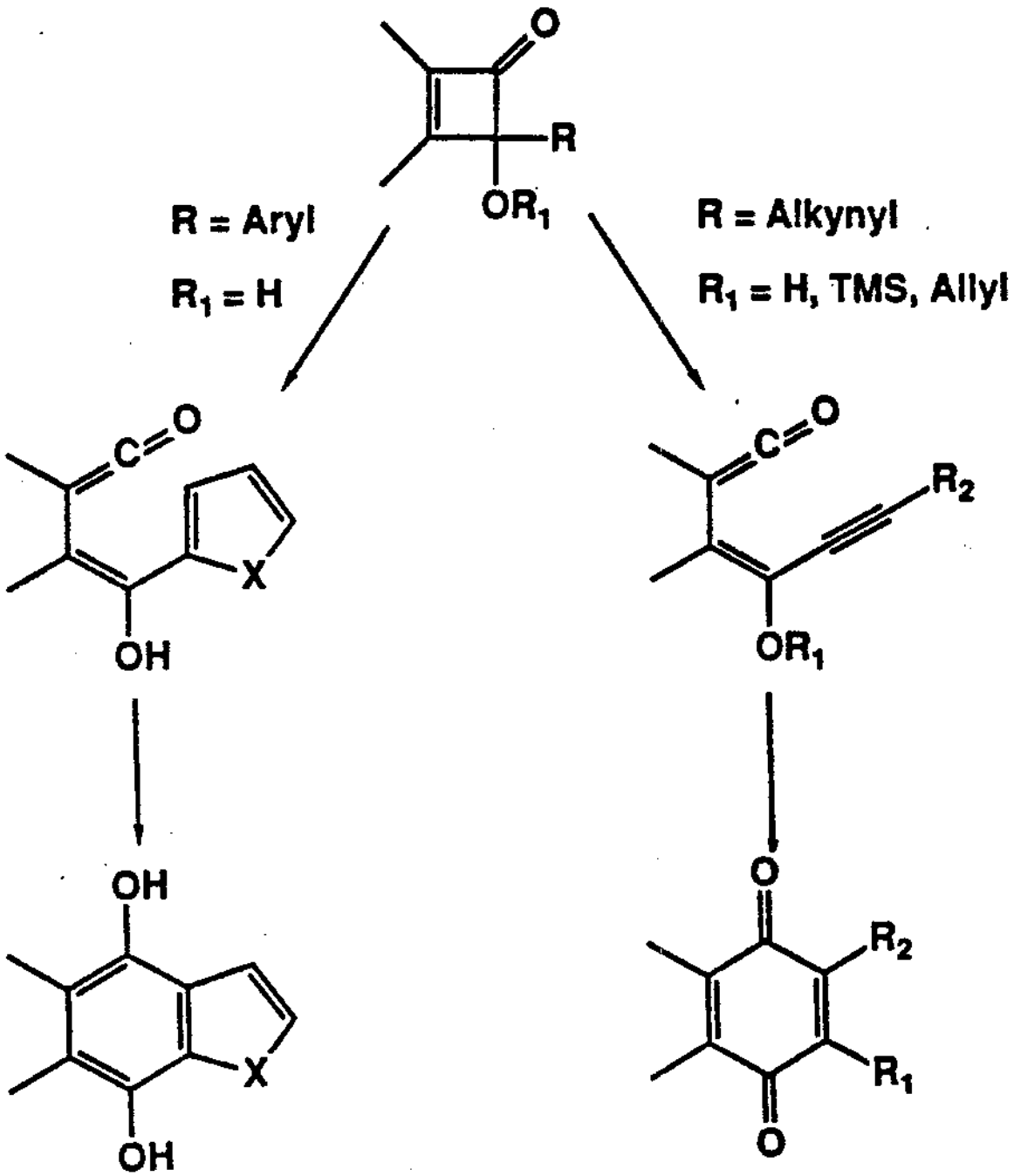
on the sp-hybridized carbon of the ketene to give a stabilized dipolar intermediate, and the subsequent cyclization of this intermediate to give the cycloadduct as illustrated with the following example.



In sharp contrast to the extensively studied intermolecular cycloaddition reactions of ketenes with unsaturated compounds, there are only some scattered reports in the literature on intramolecular ketene cycloadditions. Furthermore, most all of these reports are on photochemical or pyrolysis reactions which suffer from uncommon starting materials and complicated reaction conditions (84, 85, 86, 87, 88, 89, 90). A few recent reports which describe the six-electron electro-

cyclic reactions of some conjugated ketenes to generate a series of phenol, hydroquinone and quinone derivatives have been the only related examples that are directed toward synthetic applications (29, 91, 92).

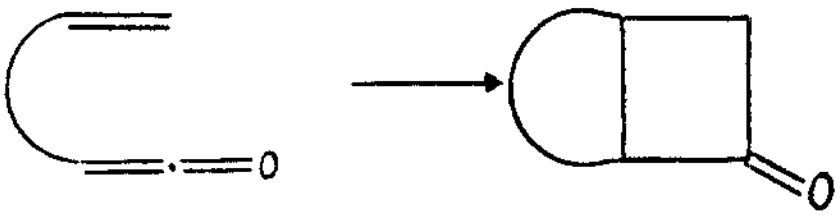




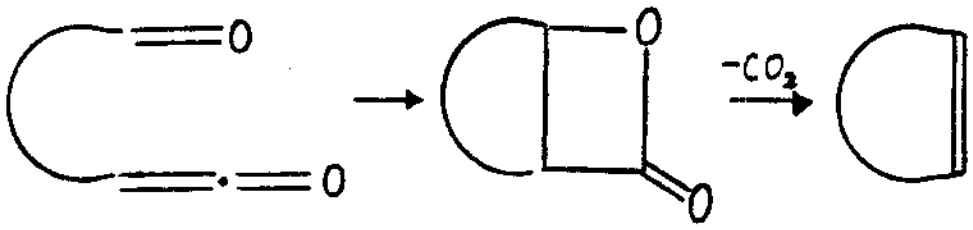
Conversely, interest and publications in the area of intramolecular Diels-Alder reactions, where the diene and the

dienophile are constrained in the same molecule, has recently increased exponentially (93, 94, 95). It is anticipated that intramolecular ketene cycloaddition reactions can be used effectively to synthesize a wide variety of interesting bridged polycyclic compounds.

In general, an intramolecular ketene olefin [2+2] cycloaddition reaction should result in the simultaneous formation of two rings.



An intramolecular ketene carbonyl [2+2] cycloaddition reaction should result in a bicyclic β-lactone or, by decarboxylation, a cycloalkene.



Both of these types of reactions are expected to lead to the formation of polycyclic systems that would be difficult to synthesize by most conventional methods.

The intramolecular cycloadditions should profit from

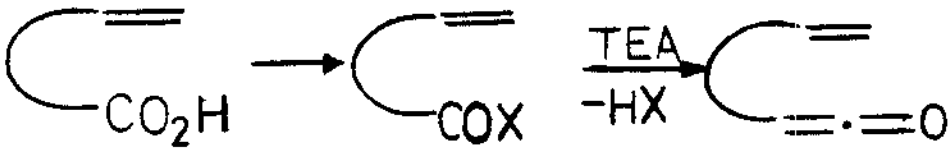
entropy factors due to the spatial proximity of the reaction partners and it is expected that intramolecular cycloadditions will favorably compete with the usually fast oligomerization of the ketene and that intramolecular reactions will occur more readily and smoothly than the corresponding intermolecular reactions. It is anticipated that intramolecular cycloadditions will be optimal when the ketene function and the ketenophile are linked by a bridge of three or four atoms so that a five- or six-membered ring will be formed along with the [2+2] cycloaddition which yields the four-membered ring. The longer and more flexible this bridge, the more the conditions resemble those for bimolecular addition. Clearly, the ease of the intramolecular cycloaddition will be a function of the length of the bridge between the ketene function and the ketenophile. It is also anticipated that intramolecular cycloaddition reactions, in general, will take place under considerably milder conditions than are required for the analogous bimolecular reactions. Consequently, ketenophiles should be more reactive in an intramolecular reaction than in an intermolecular reaction. While activated olefins (e.g., silyl enol ether, ketene acetals, cyclopentadiene, etc.) undergo intermolecular [2+2] cycloaddition readily with most ketenes (45, 46, 64, 68, 96, 97, 98, 99, 100, 101), some sterically hindered olefins only give moderate to poor yields for the intermolecular cycloaddition even with dichloroketene (102). It is anticipated that the entropy-assisted intramo-

lecular [2+2] cycloaddition should proceed in many cases where the intermolecular counterpart does not occur.

The intermolecular cycloaddition of ketenes to carbonyl compounds is significantly different from the corresponding cycloaddition to olefinic compounds. Elevated temperatures, Lewis acid catalysts, or activation of the carbonyl group is usually required for intermolecular ketene carbonyl compound cycloadditions (103, 104, 105, 106, 107, 108). However, the features of intermolecular cycloaddition may change drastically in the intramolecular counterpart due to the proximity effect. Other factors such as electronic and steric effects may function differently in intramolecular cycloadditions, and consequently, the regio- and stereochemistry could be even more interesting. Due to the difference in chemical environment between inter- and intramolecular cycloaddition, some favorable driving force or frontier orbital overlap could become more important when considering intramolecular cycloadditions than intermolecular cycloadditions as demonstrated by the above mentioned six-electron electrocyclic reactions.

It should be noted that any approach to the intramolecular cycloaddition precursors should eventually provide the difunctional compounds, i.e., molecules containing both ketene functionality and ketenophile, or their equivalents without serious conflicts during the course of the synthesis. The most obvious compatible difunctional precursors are unsa-

turated carboxylic acids with a 3 or 4 atom bridge between the two functional groups. Consequently, the reaction sequence from unsaturated carboxylic acid to unsaturated acid halide followed by triethylamine-promoted dehydrohalogenation to generate the difunctional precursor was the initial approach to this study.



In summary, the objective of this research project was to explore intramolecular ketene cycloadditions with the anticipated results of developing new synthetic methodology for the synthesis of polycyclic compounds difficult to obtain by other procedures.

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CHAPTER II

EXPERIMENTAL

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a 60 MHz Hitachi Perkin-Elmer R-24B spectrometer, employing deuteriochloroform or dimethyl-d6 sulfoxide as the solvent with tetramethylsilane as the internal standard. The ^{13}C-NMR spectra were determined at 90 MHz on a JEOL-FX-90Q FT nuclear magnetic resonance spectrometer equipped with a JEC-980B computer. Deuteriochloroform or dimethyl-d6 sulfoxide was used as a lock solvent and as the internal standard, and all chemical shifts are reported in parts per million (ppm). The infrared (IR) spectra were obtained on a Perkin-Elmer 1330 spectrometer using neat samples, solutions (taken from nmr samples) or fluorolube oil films. Chromatographic separations were performed on Davisil silica gel 62, Davison Chemical, or Aldrich silica gel, 70-270 mesh using ethyl acetate-hexane as eluent. Preparative TLC separations were performed on Aldrich pre-coated TLC plates (250 μm thick 2-25 μm silica gel on glass) using ethyl acetate-hexane as the developing solvent. The GC/MS spectra were obtained on a Hewlett Packard 5790A Series GC/Mass spectrophotometer. All melting points were determined on a Thomas Hoover capillary melting point

apparatus and, like boiling points, are uncorrected. Elemental analyses were carried out by Midwest Microlab, Indiana. High-resolution mass spectra were obtained at the Midwest Center for Mass Spectrometry, Department of Chemistry, University of Nebraska, Lincoln, Nebraska.

Hexane, benzene, tetrahydrofuran, ether and triethylamine were dried and purified by distillation from a sodium-potassium alloy under a nitrogen atmosphere prior to use. Dimethyl sulfoxide (DMSO) and N,N-Dimethylformamide (DMF) were distilled from BaO and stored over molecular sieve 4A. All reagents were distilled or recrystallized prior to use.

Intramolecular [2+2] Cycloadditions of Phenoxyketenes to Carbon-Carbon Double Bonds

Starting Materials. o-Allylphenol, o-propenylphenol, and the haloacids were commercially available. o-Vinylphenol was prepared by a literature procedures (1, 2).

o-(1-Phenylvinyl)phenol. To a Grignard solution prepared from 17.3 g (0.11 m) of bromobenzene, 2.9 g (0.12 g. atom) of magnesium, and 100 mL of THF was added 6.8 g (0.05 m) of o-hydroxyacetophenone in 50 mL of THF with efficient

stirring and cooling. The resulting solution was refluxed for 6 h and was then condensed to ca. 75 mL on a rotatory evaporator, cooled, and treated with 100 mL of 15 % aqueous acetic acid at 0 °C. The organic layer was separated, and the aqueous layer extracted with two 75-mL portions of benzene. The combined organic solution was washed with a small amount of aqueous sodium bicarbonate followed by saturated brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent resulted in 9.7 g (91 %) of sufficiently pure 1-phenyl-1-(2'-hydroxyphenyl)ethanol as white crystals: mp 110-111.5 °C; ^{1}H-NMR ($CDCl_3$), δ, 7.82-6.78 (m, 11 H), 2.23 (s, 3 H); ^{13}C-NMR ($CDCl_3$), δ, 155.0 (s), 147.0 (s), 131.4 (s), 128.0 (d), 127.3 (d), 126.4 (d), 126.2 (d), 124.9 (d), 118.6 (d), 116.4 (d), 77.0 (s), 29.8 (q); IR ($CDCl_3$), 3650-2500, 1603, 1583 cm^{-1}. The alcohol was dissolved in 50 mL of benzene to which 50 mg of iodine was added. This mixture was refluxed overnight and then cooled and washed with aqueous sodium thiosulfate. Upon drying and removal of the solvent a quantitative yield of o-(1-phenyl-vinyl)phenol was obtained as a pale yellow oil: IR (neat), 3570, 1620, 1582 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 7.34-6.77 (m, 9 H), 5.67 (s, 1 H), 5.44 (s, 1 H), 5.24 (s, 1 H),; ^{13}C-NMR ($CDCl_3$), δ, 152.9 (s), 145.0 (s), 139.3 (s), 130.3 (d), 129.2 (d), 128.3 (d), 128.2 (d), 127.5 (s), 126.7 (d), 120.2 (d), 116.3 (t), 115.7 (d).

General Procedure for (o-Alkenylphenoxy)acetic Acid Preparation.

Method A. This method utilizes water as a solvent and was used for the preparation of 2a, 3a, and 8a (Table I, p.65, 66). To a mixture of equal equivalents (30 mmol) of the o-alkenylphenol and α-chlorocarboxylic acid in 15 mL of water was slowly added with cooling and stirring 20 mL of a cold aqueous solution containing 65 mmol of NaOH. The mixture was stirred for 20 min and then refluxed for 4-16 h. Upon cooling, the solution was acidified to pH 1 with dilute HCl and extracted with two 30-mL portions of benzene. The combined benzene extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated under vacuum to yield the crude acid as an oil which was purified by recrystallization from hexane.

Method B. This method utilizes THF as a solvent and was used for the preparation of 1a, 4a, 5a, 6a, 7a, and 9a (Table I, p.65, 66). To a mixture of equal equivalents * (30 mmol) of the o-alkenylphenol and α-halo carboxylic acid in 30 mL of THF was slowly added with cooling and stirring 65 mmol ** of sodium hydride as an 80 % dispersion in mineral oil. The mixture was stirred for 20 min and then refluxed for 4-16 h. The solution was cooled and acidified to pH 1

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* To simplify the purification, 35 mmol of o-propenylphenol was used for 5a.

** To avoid the isomerization of o-allylphenol to o-propenylphenol, 60 mmol of sodium hydride was used for 9a.

with dilute HCl. An 80-mL portion of benzene and 20 mL of saturated brine was added to this solution. The organic layer was washed with four portions of 10 mL of saturated brine, dried over anhydrous magnesium sulfate, and evaporated under vacuum to yield the crude acids. Compounds 1a, 4a, 5a, and 9a were purified by recrystallization from hexane and the others by column chromatography using silica gel (20 % EtOAc-hexane).

2-(o-Vinylphenoxy)propanoic Acid, 1a. A 4.3 g (75 % yield) portion of this acid was obtained with mp 105-106 °C; IR ($CDCl_3$), 3650-2300, 1703, 1625 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 11.24 (s, 1 H), 7.19-5.16 (m, 7 H), 4.53 (q, 1 H, J=5.4 Hz); ^{13}C-NMR ($CDCl_3$), δ, 178.4 (s), 154.4 (s), 72.5 (d), 8.4 (q).

(o-Propenylphenoxy)acetic Acid, 2a. A 3.5 g (61 % yield) portion of this acid was obtained with mp 101-102 °C; IR (DMSO-d6), 3650-2250, 1710, 1628 cm^{-1}; ^{1}H-NMR (DMSO-d6), δ, 9.61 (s, 1 H), 7.63-5.69 (m, 6 H), 4.69 (s, 2 H), 1.91 (m, 3 H); ^{13}C-NMR (DMSO-d6), δ, 169.2 (s), 153.2 (s), 63.9 (t), 17.6 (q).

2-(o-Propenylphenoxy)propanoic Acid, 3a. A 3.3 g (54 % yield) portion of this acid was obtained with mp 95-97 °C; IR ($CDCl_3$), 3680-2200, 1705, 1634 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 11.05 (s, 1 H), 7.55-5.65 (m, 6 H), 4.63 (q, 1 H, J=5.3 Hz), 1.86 (m, 6 H); ^{13}C-NMR ($CDCl_3$), δ, 178.1 (s), 153.9 (s), 72.6 (d), 18.7 (q), 18.2 (q).

2-(o-Propenylphenoxy)butanoic Acid, 4a. A 5.8 g (88 %

yield) portion of this acid was obtained with mp 105-106 °C; IR ($CDCl_3$), 3600-2300, 1697, 1632 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 11.05 (s, 1 H), 7.55-5.65 (m, 6 H), 4.59 (t, 1 H, J=6 Hz), 1.91 (m, 2 H), 1.18 (t, 3 H, J=6 Hz); ^{13}C-NMR ($CDCl_3$), δ, 177.6 (s), 154.1 (s), 77.5 (d), 26.0 (t), 18.7 (q), 95 (q).

(o-Propenylphenoxy)phenylacetic Acid, 5a. A 6.4 g (79 % yield) portion of this acid was obtained with mp 156-159 °C; IR ($CDCl_3$), 3700-2700, 1720, 1645 cm^{-1}; ^{1}H-NMR (DMSO-d6), δ, 7.62-5.84 (m, 11 H), 5.47 (s, 1 H), 1.72 (d, 3 H, J = 6 Hz); ^{13}C-NMR (DMSO-d6), δ, 171.0 (s), 153.9 (s), 136.3 (s), 78.4 (d), 18.9 (q).

o-(1-Phenylvinyl)phenoxyacetic Acid, 6a. A 6.2 g (71 % yield) portion of this acid was obtained as a pale yellow oil; IR ($CDCl_3$), 3700-2380, 1710, 1623 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 9.53 (s, 1 H), 7.65-6.63 (m, 9 H), 5.60 (s, 1 H), 5.25 (s, 1 H), 4.28 (s, 2 H), ^{13}C-NMR ($CDCl_3$), δ, 172.8 (s), 155.0 (s), 146.5 (s), 75.6 (t).

2-[o-(1-Phenylvinyl)phenoxy]propanoic Acid, 7a. A 5.6 g (70 % yield) portion of this acid was obtained as a pale yellow oil; IR (neat), 3600-2250, 1723, 1612 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 10.41 (s, 1 H), 7.45-6.67 (m, 9 H), 5.71 (s, 1 H), 5.42 (d, 1 H, J = 2.8 Hz), 4.62 (q, 1 H, J = 5.4 Hz), 1.31 (d, 3 H, J = 5.4 Hz); ^{13}C-NMR ($CDCl_3$), δ, 176.8 (s), 154.5 (s), 146.9 (s), 141.3 (s), 72.6 (d), 17.6 (q).

2-(o-Allyphenoxy)propanoic Acid, 8a. A 3.1 g (50 % yield) portion of this acid was obtained with a mp of 62-64

°C; IR ($CDCl_3$), 3680-2250, 1710, 1629 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ,10.53 (s, 1 H), 6.96-6.29 (m, 4 H), 6.17-5.52 (m, 1 H), 5.24-4.45 (m, 3 H), 3.23 (d, 2 H, J=5.6 Hz), 1.44 (d, 3 H, J=5.5 Hz); ^{13}C-NMR ($CDCl_3$), δ, 177.8 (s), 154.8 (s), 136.6 (d), 129.0 (s), 72.0 (d), 34.1 (t), 18.1 (q).

2-(o-Allylphenoxy)butanoic Acid, 9a. A 5.3 g (81 % yield) portion of this acid was obtained with mp 53-55 °C; IR ($CDCl_3$) 3700-2230, 1715, 1630 cm-1; ^{1}H-NMR ($CDCl_3$), δ, 10.56 (s, 1 H), 7.18-6.46 (m, 4 H), 6.31-5.56 (m, 1 H), 5.21-4.95 (m, 1 H), 4.95-4.76 (m, 1 H), 4.52 (t, 1 H, J = 5.9 Hz), 3.48 (d, 2 H, J=6 Hz), 2.00 (m, 2 H), 1.21 (t, 3 H, J=6.8 Hz); ^{13}C-NMR ($CDCl_3$), δ, 177.6 (s), 155.2 (s), 136.8 (d), 129.1 (s), 76.6 (d), 34.3 (t), 26.0 (t), 9.4 (q).

General Procedure for Intramolecular Cycloaddition.

Method A. This method utilized acid chlorides to generate the corresponding ketenes and was used for the preparation of 1b through 9b (Table I, p.65, 66). The (o-alkenylphenoxy)acetic acids were converted to the corresponding acid chlorides by reaction with 5-8 eq. of oxalyl chloride in benzene at ambient temperature for 3 h. The excess oxalyl chloride was removed under vacuum and the crude acid chloride diluted with benzene and slowly added to a solution of 2 eq. of triethylamine in benzene at gentle reflux. The addition was usually over a period of 2-6 hr. and the total amount of solvent was 300-450 mL for a 5-10

mmol preparation. (In some instances, such as 8b and 9b, where the olefin functionality is not very reactive toward the cycloaddition process, it would be necessary to keep an even lower concentration of the reacting ketene.) After the addition was complete, the mixture was gently refluxed for 4-8 h. Upon cooling, the salt was removed by filtration and the solvent and excess amine were removed under reduced pressure. The crude cycloaddition product was purified by recrystallization from hexane (5b, 8b) or by column chromatography using silica gel (2-7% EtOAc-hexane; 1b, 2b, 3b, 4b, 6b, 7b, 9b).

Method B. This method utilized acyl tosylates to generate the ketenes and was tried for 5b and 8b (Table V, p. 95). A 5 mmol-portion of (o-alkenylphenoxy)acetic acid in 50 mL of benzene was added over 5 h through a syringe to a refluxing solution of 4 equiv of triethylamine and 2 equiv of p-toluenesulfonyl chloride in 50 mL of benzene. After the addition was complete, the mixture was gently refluxed for 6 h. Upon cooling, the reaction mixture was washed with three 50-mL portions of water and then concentrated in vacuo to a volume of about 30 mL. This concentrate was stirred with 250 mL of 3 % aqueous NaOH solution for 10 h to remove excess tosyl chloride. The benzene layer was dried (anhydrous magnesium sulfate), filtered, and then the benzene evaporated under reduced pressure. The residue was purified by column chromatography

using a silica gel column as described above for Method A.

1-Methyl-2-oxa-3,4-benzobicyclo[3.2.0]heptan-7-one, 1b.

A 0.54-g (60 % yield) portion of 1b was obtained from 1 g of 1a with mp 49-50 °C; IR ($CDCl_3$), 1784, 1612, 1593 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 7.23-6.60 (m, 4 H), 3.70-2.76 (m, 3 H), 1.58 (s, 3 H); ^{13}C-NMR ($CDCl_3$), δ, 207.3 (s), 160.1 (s), 128.8 (s), 128.6 (d), 125.4 (d), 121.5 (d), 109.9 (d), 102.3 (s), 53.7 (t), 39.9 (d), 15.9 (q).

Anal. Calcd. for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.56; H, 5.86.

6-Methyl-2-oxa-3,4-benzobicyclo[3.2.0]heptan-7-one, 2b.

A 0.65-g (72 % yield) portion of 2 b was obtained from 1 g of 2a with a mp of 65-66 °C; IR ($CDCl_3$), 1781, 1608, 1589 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 7.15-6.58 (m, 4 H), 5.63-5.36 (m, 1 H), 4.23-3.38 (m, 2 H), 1.21 (d, exo-Me, J=7.3 Hz), 0.84 (d, endo-Me, J=7.3 Hz); ^{13}C-NMR ($CDCl_3$), δ, 2.08.6 (s), 161.1 (s), 128.7 (d), 127.0 (d), 125.2 (s), 121.2 (d), 110.6 (d), 91.9 (d), 59.0 (d), 39.9 (d), 8.6 (q).

Anal. Calcd. for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.64; H, 5.70.

1,6-Dimethyl-2-oxa-3,4-benzobicyclo[3.2.0]heptan-7-one, 3b. A 0.69-g (76 % yield) portion of 3b was obtained from 1 g of 3a with mp 69-70 °C; IR ($CDCl_3$), 1778, 1609, 1590 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 7.08-6.87 (m, 4 H), 3.83-3.81 (m, 2 H), 1.66 (s, 3 H), 0.96 (d, 3 H, J=6.6 Hz); ^{13}C-NMR ($CDCl_3$), δ, 210.5 (s), 160.7 (s), 128.6 (d), 126.9 (d), 124.5 (s), 121.0

(d), 110.4 (d), 100.2 (s), 57.3 (d), 45.1 (d), 16.3 (q), 8.4 (q).

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.51; H, 6.39.

1-Ethyl-6-methyl-2-oxa-3,4-benzobicyclo[3.2.0]heptan-7-one, 4b. A 1.31-g (71 % yield) portion of a colorless oil was obtained from 2 g of 4a; IR (Neat), 1781, 1608, 1590 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 7.10-6.45 (m, 4 H), 3.84-0.79 (m, 10 H); ^{13}C-NMR ($CDCl_3$), δ, 210.4 (s), 160,8 (s), 128.4 (d), 126.7 (d), 124.4 (s), 120.8 (d), 110.1 (d), 104.0 (s), 57.5 (d), 42.9 (d), 23.2 (t), 8.3 (q), 7.4 (q).

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.98; H, 6.78.

6-Methyl-2-oxa-1-phenyl-3,4-benzobicyclo[3.2.0]heptan-7-one, 5b. A 1.6-g (85 % yield) portion and a 0.9-g (83 % yield) portion of 5 b were obtained from 2 g and 1.2 g, respectively, of 5a by Method A and Method B with a mp of 95-96 °C; IR (film), 1783, 1611, 1592 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 7.65-6.86 (m, 9 H), 4.50-3.76 (m, 2 H), 1.19 (d, 3 H, J=6 Hz); ^{13}C-NMR ($CDCl_3$), δ, 208.4 (s), 160.7 (s), 133.5 (s), 129.0 (d), 128.8 (d), 126.9 (s), 126.1 (d), 121.5 (d), 110.8 (s), 59.2 (d), 46.1 (d), 8.7 (q).

Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.40; H, 5.61.

2-Oxa-5-phenyl-3,4-benzobicyclo[3.2.0]heptan-7-one, 6b. A 1.31-g (88 % yield) portion of 6b was obtained from 1.6 g

of 6a with mp 162-163 °C; IR ($CDCl_3$), 1789, 1608, 1590 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 8.32-7.41 (m, 9 H), 6.37 (t, 1 H, J=2.5 Hz), 4.71 (dd, 1 H, J=16.2, 2.5 Hz), 4.22 (dd, 1 H, J=16.2, 2.5 Hz); ^{13}C-NMR ($CDCl_3$), δ,203.9 (s), 142.0 (s), 131.7 (s), 129.3 (d), 128.8 (d), 127.2 (d), 126.1 (d), 12.5 (d), 122.7 (d), 111.1 (d), 99.5 (d), 59.3 (t), 50.7 (s).

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.11; H, 4.95.

1-Methyl-2-oxa-5-phenyl-3,4-benzobicyclo[3.2.0]heptan-7-one, 7b. A 2.35-g (84 % yield) portion of colorless oil was obtained from 3 g of 7a; IR (neat), 1788, 1718, 1658, 1593 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 8.16-7.35 (m, 9 H), 4.86 (d, 1 H, J=16.4 Hz), 4.03 (d, 1 H, J=16.4 Hz), 2.05 (s, 3 H); ^{13}C-NMR ($CDCl_3$), δ, 207.1 (s), 159.9 (s), 138.5 (s), 133.1 (d), 129.0 (d), 128.4 (d), 127.5 (d), 127.0 (d), 125.7 (d), 122.3 (d), 110.5 (d), 104.1 (s), 55.5 (t), 53.2 (s), 13.4 (q).

Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.35; H, 5.65.

1-Methyl-2-oxa-3,4-benzobicyclo[4.2.0]octan-8-one, 8b. A 0.39-g (43 % yield) portion and a 0.54-g (50 % yield) portion of 8b were obtained from 1 g and 1.2 g, respectively, of 8a with mp 65-66 °C; IR ($CDCl_3$), 1777, 1610, 1591 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 7.07-6.84 (m, 4 H), 3.05-2.17 (m, 5 H), 1.48 (s, 3 H); ^{13}C-NMR ($CDCl_3$), δ, 209.9 (s), 154.6 (s), 129.1 (d), 127.5 (s), 123.8 (d), 122.2 (d), 117.3 (d), 92.6 (s), 46.9 (t), 34.4 (d), 28.2 (t), 19.5 (q).

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.65; H, 6.47.

1-Ethyl-2-oxa-3,4-benzobicyclo[4.2.0]octan-8-one, 9b.

A 0.45-g (49 % yield) portion of a colorless oil was obtained from 1 g of 9a; IR (Neat), 1780, 1605, 1583 cm^{-1}; ^1H-NMR ($CDCl_3$), δ, 7.04-6.89 (m, 4 H), 2.84-2.17 (m, 5 H, 1.72 (q, 2 H, J=4.8 Hz), 0.92 (t, 3 H, J=4.8 Hz); ^{13}C-NMR ($CDCl_3$), δ, 209.9 (s), 154.8 (s), 129.06 (d), 127.49 (d), 123.86 (s), 122.0 (d), 117.3 (d), 95.8 (s), 47.0 (t), 32.5 (d), 28.5 (t), 26.3 (t), 7.06 (q).

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.44; H, 7.15.

Intramolecular [2+2] Cycloadditions of Keteniminium Salts to Carbon-Carbon Double Bonds

Starting Materials. o-Allylphenol, 3-chloropropanoic acid, and 1,4-dibromobutane were commercially available. The haloamides and (o-allylphenoxy)acetic acid (needed for 13a in Table II, p.72) were prepared by literature procedures (3, 4, 5, 6). 5-(Ethoxycarbonylmethyl)cyclooctanone and 8-(ethoxycarbonylmethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-11-one were synthesized by Wu (7). (o-Alkenylphenoxy)acetic acids 9a, 7a, and 5a (needed for 10a, 11a, and 12a, respectively, in Table II, p.72) were prepared previously in this study.

3-(o-Allylphenoxy)propanoic Acid. To a solution of 10.9 g (0.1 mol) of 3-chloropropanoic acid in 20 mL of ice water was added with cooling and stirring a solution of 4 g (0.1 mol) of NaOH in 20 mL of ice water. The resulting cold solution was stirred for 20 min and added dropwise to a refluxing aqueous solution containing 0.09 mol of sodium o-allylphenolate (prepared from 12.1 g of o-allylphenol and 4 g of NaOH) and 30 mL of water. After the addition was complete, the reaction mixture was refluxed for an additional 15 h. Upon cooling, the aqueous solution was washed with three 20-mL portions of chloroform. The aqueous solution was then acidified to pH 1 with dil. HCl and extracted with

three 30-mL portions of ether. The combined ether extracts were washed with water and brine, dried over anhydrous magnesium sulfate and evaporated in vacuo. A 5.13-g (28 %) portion of pure acid was obtaind as white solid: mp 98-100 °C; IR ($CDCl_3$), 3060, 1710, 1638 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 10.53 (s, 1 H), 7.04-6.38 (m, 4 H), 6.22-5.65 (m, 1 H), 5.35-4.60 (m, 4 H), 3.56-3.27 (m, 4 H); ^{13}C-NMR ($CDCl_3$), δ, 177.3 (s), 156.1 (s), 137.8 (d), 129.8 (d), 128.3 (s), 127.0 (d), 120.4 (d), 114.8 (t), 111.3 (d), 64.5 (t), 41.8 (t), 34.0 (t).

5-(o-Allylphenoxy)pentanoic Acid. A mixture of sodium o-allylphenolate (37 mmol, prepared from 5.1 g of o-allylphenol and 2.1 g of 60 % sodium hydride in mineral oil) and 1,4-dibromobutane (24.2 g, 0.11 mol) in 30 mL of THF was refluxed for 8 h. The reaction mixture was cooled and filtered. The filtrate was evaporated and vacuum distilled to give 6.8 g (68 %, bp 85-90 °C/0.03 mm Hg) of 1-allyl-2-(4'-bromobutoxy)benzene. This bromo- compound was reacted with potassium cyanide followed by basic hydrolysis according to the standard procedure (8, 9) to give the crude acid. A 4.4-g (75 %) portion of pure acid as a pale yellow oil was obtained via a silica gel column filtration: IR (neat), 3065, 1700, 1635 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 9.95 (s, 1 H), 7.18-5.46 (m, 5 H), 4.85 (s, 1 H), 4.63 (s, 1 H), 3.59-1.70 (m, 10 H); ^{13}C-NMR ($CDCl_3$), δ, 179.3 (s), 156.3 (s), 136.8 (d), 129.5 (d), 128.4 (s), 127.0 (d), 120.2 (d), 115.0 (t), 110.9 (d), 67.0 (t), 34.1 (t), 33.3 (t), 28.4 (t), 21.2 (t).

6-Oxo-6-phenylhexanoic acid, 20c. This acid was prepared in 67 % (90 % for the Grignard Reaction step, the intermediate product being 1-phenylcyclohexanol, and 74 % for the following oxidation step) overall yield by a procedure reported for the preparations of some other keto acids (10, 11): mp 71-73 °C; IR (film), 3300-2550, 1695, 1682 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 10.37 (s, 1 H), 7.93 (m, 2 H), 7.67-7.43 (m, 3 H), 3.13-2.96 (m, 2 H), 2.54-2.38 (m, 2 H), 1.88-1.66 (m, 4 H); ^{13}C-NMR ($CDCl_3$), δ, 199.8 (s), 179.4 (s), 136.8 (s), 132.9 (d), 128.4 (d, 2C), 127.9 (d, 2C), 37.9 (t), 33.8 (t), 24.2 (t), 23.5 (t).

1-Allylcyclopentanol. This alcohol was prepared from allyl bromide and cyclopentanone by standard Grignard Reaction in 75 % distilled yield: bp 45-47 °C (2.5 mm Hg); IR (neat), 3400, 3080, 1638 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 6.17-5.74 (m, 2 H), 5.22-4.98 (m. 2 H), 2.38-1.42 (m, 10 H); ^{13}C-NMR ($CDCl_3$), δ, 134.5 (d), 118.0 (t), 81.2 (s), 45.6 (t), 39.2 (t), 23.7 (t).

(1'-Allylcyclopentanoxy)acetic Acid. This acid was prepared from 1-allylcyclopentanol and bromoacetic acid by the procedure previously described for (o-alkenylphenoxy)-acetic acids (Method B) in 83 % yield as a pale yellow oil. IR (neat), 3095, 1733, 1640 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 10.57 (s, 1 H), 5.68-5.92 (m, 1 H), 5.13 (m, 2 H), 4.05 (s, 2 H), 2.39 (d, 2 H, J = 6.4 Hz), 1.84-1.56 (m, 8 H); ^{13}C-NMR ($CDCl_3$), δ, 172.2 (s), 133.4 (d), 118.0 (t), 88.7 (s), 60.2

(t), 40.9 (t), 35.8 (t), 23.7 (t).

5-Oxocyclooctylacetic Acid, 22c. A mixture of 5-(ethoxycarbonylmethyl)cyclooctanone (1.06 g, 5.0 mmol), sodium hydroxide (2.0 g) and water (50 mL) was heated at 70 °C for 24 h. The reaction mixture was then cooled and washed with chloroform (3 x 30 mL). The aqueous layer was acidified to pH 1 with dil. HCl at 5 °C and extracted with ether (4 x 40 mL). The combined ether extracts were dried over anhydrous magnesium sulfate and evaporated under vacuum to give the crude keto acid. A 0.80-g (87 %) portion of the pure keto acid was obtained via column chromatography on silica gel (25-30 % EtOAc-hexane) as white solid: mp 82-83 °C; IR (Film), 3200, 1725, 1690 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 10.30 (s, 1 H), 2.64-1.42 (m, 15 H); ^{13}C-NMR ($CDCl_3$), δ, 217.6 (s), 177.6 (s), 42.8 (t), 41.9 (d), 33.5 (t), 32.9 (t), 24.7 (t); GC/MS (70 eV), m/e (relative intensity), 184.1 (molecular ion, 4.8), 166.0 (7.2) 156.1 (14.4), 124.1 (21.7), 97.1 (46.3), 41.0 (100.0).

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.16; H, 8.57.

11-Oxopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecyl-8-acetic Acid, 23c. A 2.46-g (10.0 mmol) portion of 8-(ethoxycarbonylmethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-11-one was treated in the same manner as was for 5-oxocyclooctylacetic acid to give 1.75 g (81 %) of the ketoacid as white solid: mp 108-109 °C; IR (film), 3440, 1730, 1695 cm^{-1}; ^{1}H-NMR ($CDCl_3$),

δ, 10.30 (s, 1 H), 2.52-2.18 (m, 11 H), 1.60 (AB, J=12.5 Hz, 1 H), 1.33 (AB, J=12.5 Hz, 1 H); ^{13}C-NMR ($CDCl_3$), δ, 218.0 (s), 174.0 (s), 51.0 (t), 50.0 (d), 47.8 (d), 43.1 (d), 42.3 (d), 41.8 (d), 41.6 (d), 39.0 (d), 36.8 (d), 35.4 (d), 31.5 (t); GC/MS (70 eV), m/e (relative intensity), 219.0 (3.6), 218.1 (molecular ion, 23.0), 200.1 (25.5), 172.0 (100.0), 129.0 (41.9), 124.0 (77.7), 91.0 (62.8).

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.23; H, 6.59.

Preparation of Alkenoic Acids by Wittig Reaction (Table III, p.80).

6-Phenyl-6-heptenoic Acid, 20d. To 2.73 g (7.63 mmol) of methyl triphenylphosphonium bromide in 15 mL of dry DMSO under nitrogen and at ambient temperature was added dropwise with stirring 7.1 mL (1.0 M solution in Hexane) of n-butyllithium over 10 min. The mixture was stirred at room temperature for an additional 1.5 h. A solution of 582 mg (2.82 mmol) of 20c in 10 mL of DMSO was added dropwise to the ylide over 30 min. The mixture was then heated at 60 °C for an additional 10 h. Upon cooling, the reaction mixture was quenched with 80 mL of water and washed with three 20-mL portions of chloroform. The aqueous solution was acidified to pH 1 in the cold and extracted with four 30-mL portions of ether. The combined ether extracts were washed with brine, dried over anhydrous magnesium sulfate and evaporated under

vacuum. The residue was passed through a silica gel column using 20-25 % EtOAc-hexane as the eluent to give 409 mg (71 %) of pure 20d as white solid: mp 44-47 °C; IR ($CDCl_3$), 3600-2300, 1703, 1625 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 10.36 (s, 1 H), 7.33-7.25 (m, 5 H), 5.26 (s, 1 H), 5.05 (s, 1 H), 2.50-1.53 (m, 8 H); ^{13}C-NMR ($CDCl_3$), δ, 180.1 (s), 148.0 (s), 141.1 (s), 128.2 (d), 127.3 (d), 126.0 (d), 112.4 (t), 34.9 (t), 33.8 (t), 27.5 (t), 24.2 (t); GC/MS (70 eV), m/e (relative intensity), 205.2 (1.8), 204.2 (molecular ion, 12.4), 144.2 (18.5), 131.2 (18.7), 118.1 (100.0), 91.1 (25.3), 77.1 (19.4).

Anal. Calcd. for $C_{13}H_{16}O_2$: $\underline{M}_r$ 204.1151. Found (high-resolution mass spectrometry): $\underline{M}_r$ 204.1156.

5-Methylenecyclooctylacetic Acid, 22d. The same Wittig Reaction procedure as for 20c --> 20d afforded 552 mg (79 %, as a pale yellow oil) of 22d from 706 mg (3.84 mmol) of 22c; IR (neat), 3060, 1705, 1638 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 10.30 (s, 1 H), 4.74 (s, 2 H), 2.66-1.44 (m, 15 H); ^{13}C-NMR ($CDCl_3$), δ, 177.5 (s), 151.2 (s), 111.6 (t), 43.1 (t), 40.3 (d), 35.4 (t), 32.8 (t), 26.4 (t); GC/MS (70 eV), m/e (relative intensity), 182.2 (molecular ion, 5.3), 140.1 (44.2), 122.2 (35.8), 107.1 (35.0), 94.1 (97.3), 41.1 (100.0).

Anal. Calcd. for $C_{11}H_{18}O_2$: $\underline{M}_r$ 182.1307. Found (high-resolution mass spectrometry): $\underline{M}_r$ 182.1308.

11-Methylenepentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecyl-8-acetic Acid, 23d. The same Wittig Reaction procedure as for

20c --> 20d afforded 0.87 g (82 %) of 23d from 1.09 g (5.0 mmol) of 23c with mp 86-87.5 °C. IR (film), 3445, 3050, 1700, 1635 cm^{-1} ; ^{1}H-NMR ($CDCl_3$), δ, 10.70 (s, 1 H), 4.71 (d, J = 3.0 Hz, 1 H), 4.64 (d, J = 3.0 Hz, 1 H), 2.66-1.88 (m, 11 H), 1.72 (AB, J = 11.0 Hz, 1 H), 1.25 (AB, J = 11.0 Hz, 1 H); ^{13}C-NMR ($CDCl_3$), δ, 180.0 (s), 155.1 (s), 103.1 (t), 48.2 (d), 48.0 (d), 47.2 (d), 47.1 (d), 42.2 (d), 41.4 (d), 41.3 (d), 40.9 (d), 39.5 (d), 35.4 (t), 32.4 (t); GC/MS (70 eV), m/e (relative intensity), 217.1 (3.5), 216.1 (molecular ion, 33.9), 171.2 (12.2), 156.2 (28.7), 128.1 (20.9), 115.1 (30.4), 105.1 (41.7), 91.1 (100.0), 79.1 (40.0), 77.2 (45.2).

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.45; H, 7.75.

General Procedure for Unsaturated Amide Preparation.

Method A. This method was used for the preparation of all unsaturated amides except for 15a (Table II, p.72). The corresponding precursor unsaturated acids were treated with 5-8 eq. of oxalyl chloride in benzene at ambient temperature for 3-5 h. The excess oxalyl chloride was removed in vacuo and the crude acid chloride was diluted with benzene. To the acid chloride solution was added slowly with stirring and cooling 3-4 eq. of diethylamine. The mixture was stirred overnight at ambient temperature. Upon filtration, the filtrate was evaporated and passed through a silica gel column using 25 % EtOAc-hexane as the eluent. Yields of 85-

92 % were obtained for this two-step transformation. The purities and structures of these unsaturated amides were determined by TLC (one spot), IR (strong amide I band at 1635-65 cm^{-1}), ^{1}H-NMR, ^{13}C-NMR (The two ethyl groups on the nitrogen atom show four decoupled peaks.), and GC/MS.

Method B. This method was used for the preparation of unsaturated amide 15a. To a solution of 10 g (73 mmol) of o-allylphenol in 60 mL of dry THF was added 3.37 g (80 mmol) of unwashed 60 % NaH and the solution was stirred for 20 min under nitrogen. An 8.88-g (50 mmol) portion of N,N-diethyl-4-chlorobutyramide was added, and the reaction mixture was refluxed overnight. Upon cooling, 100 mL of dry hexane was added and stirred for 10 min. The salt was filtered and the filtrate evaporated. The excess o-allylphenol was removed by vacuum distillation. The crude 15a was further purified by column chromatography on silica gel (15 % EtOAc-hexane) to give 9.5 g (69 %) of pure 15a. IR (neat), 3075, 1638 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 7.23-6.56 (m, 4 H), 6.18-5.67 (m, 2 H), 5.15-4.84 (m, 3 H), 3.98 (t, J = 5.6 Hz, 2 H), 3.36 (q, J = 5.7 Hz, 4 H), 2.61-1.92 (m, 4 H), 1.12 (t, J = 7.2 Hz, 6 H); ^{13}C-NMR ($CDCl_3$), δ, 171.1 (s), 156.3 (s), 136.8 (d), 129.5 (d), 128.2 (s), 127.1 (d), 120.2 (d), 114.8 (t), 111.0 (d), 66.9 (t), 41.6 (t), 39.9 (t), 34.2 (t), 29.2 (t), 25.0 (t), 14.1 (q), 12.9 (q).

General Procedure for Intramolecular [2+2] Cycloaddi-

tions of Keteniminium Salts to Carbon-Carbon Double Bonds. All keteniminium salts were prepared and reacted by the procedure of Snider et al (12) as described for 10b. All crude hydrolyzed cycloadducts were routinely chromatographed three times; the first column chromatography on 70-270 mesh silica gel afforded spectroscopically pure products (Table II, p.72, 73) which were mostly yellow oils. The analytical samples were obtained via preparative TLC (30 % EtOAc-hexane as the developing solvent) followed by another column chromatography on silica gel (4-12 % EtOAc-hexane). The yields were reported based on the initially obtained spectroscopically pure products. Good yields were not achieved for 17b and 18b until 5 % aqueous NaOH was added to the two-phase hydrolyzing mixture (The methylene chloride was displaced by benzene.). However, 5 % aqueous NaOH would destroy such cycloadducts as 19b at ambient temperaturre but not such cycloadducts as 10b, 11b, 12b, or 13b at ambient temperature for a prolonged time.

1-Ethyl-2-oxa-3,4-benzobicyclo[4.2.0]octan-8-one, 10 b. To a solution of 10a (1.36 g, 4.95 mmol) in 80 mL of dry benzene under N_2 was added 0.74 mL (1.05 equiv) of collidine and the solution was heated at reflux. A solution of 1.02 mL (1.1 equiv) of triflic anhydride (trifluoromethanesulfonic anhydride, Tf_2O) in 15 mL of dry benzene was added over 30 min via a syringe. An orange to brownish oil gradually formed and separated. The solution was heated at reflux for

2 h, cooled to 25°C, and evaporated in vacuo. The residual oil was washed with ether and then taken up in 50 mL of CH_2Cl_2 and 50 mL of water. The two-phase mixture was stirred for 24 h at room temperature, and the methylene chloride was removed in vacuo at 10°C to leave a yellow aqueous layer containing brownish gum. This was extracted with three 40-mL portions of CCl_4. The combined CCl_4 layers were washed with water and brine. The combined aqueous layers were extracted with two 20-mL portions of CH_2Cl_2. The combined CH_2Cl_2 layers were washed with water and brine. The two fractions were combined and submitted to a silica gel column. A 317-mg (32 % yield) portion of 10b was obtained. The spectra of 10b were identical with those of 9b.

1-Methyl-5-phenyl-2-oxa-3,4-benzobicyclo[3.2.0]heptan-7-one, 11b. A 401-mg (70 % yield) portion of 11b was obtained from 738 mg of 11a. The 11b was spectroscopically identical with 7b.

6-Methyl-1-phenyl-2-oxa-3,4-benzobicyclo[3.2.0]heptan-7-one, 12b. A 469-mg (66 % yield) portion of 12b was obtained from 922 mg of 12a. The mp and spectra were identical with those of 5b.

2-Oxa-3,4-benzobicyclo[4.2.0]octan-8-one, 13b. A 0.95-g (44 % yield) portion of oil was obtained from 3.06 g of 13a. IR (neat), 1786 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 7.19-6.74 (m, 4 H), 3.21-2.16 (m, 6 H); ^{13}C-NMR ($CDCl_3$), δ, 205.8 (s), 154.0 (s), 129.1 (d) 127.5 (d), 123.1 (s), 121.9 (d), 117.0 (d),

85.3 (d), 48.0 (t), 27.8 (t), 26.2 (d); GC/MS (70 eV), m/e (relative intensity), 174.1 (molecular ion 0.8), 146.0 (1.6), 145.0 (11.7), 132.0 (62.0), 131.0 (100.0), 77.0 (11.8).

Anal. Calcd. for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.70; H, 5.73.

3-Oxa-4,5-benzobicyclo[5.2.0]nonan-9-one, 14b. A 62-mg (18 % yield) portion of oil was obtained from 479 mg of 14a. IR ($CDCl_3$), 1777 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 7.09-6.87 (m, 4 H), 3.08-2.16 (m, 8 H); ^{13}C-NMR ($CDCl_3$), δ,206.1 (s), 153.8 (s), 130.3 (d), 28.8 (d), 124.5 (s), 120.7 (d), 118.2 (d), 84.2 (t), 53.1 (d), 49.2 (t), 29.0 (t), 27.8 (d).

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found : C, 76.19; H, 6.28.

4-Oxa-5,6-benzobicyclo[6.2.0]decan-10-one, 15b. A 96-mg (10 % yield) portion of oil was obtained from 1.31 g of 15a. IR ($CDCl_3$), 1775 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 7.32-6.97 (m, 4 H), 3.35-2.21 (m, 10 H); ^{13}C-NMR ($CDCl_3$), δ, 209.1 (s), 155.9 (s), 129.9 (d), 129.2 (d), 127.1 (s), 120.5 (d), 115.0 (d), 66.3 (t), 64.7 (t), 62.9 (d), 62.5 (d), 50.4 (t), 50.0 (t), 36.5 (t), 35.6 (t), 31.5 (t), 31.3 (t), 28.7 (d), 28.5 (d).

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.99; H, 7.06.

5-Oxa-6,7-benzobicyclo[7.2.0]undecan-11-one, 16b. A 55-mg (4 % yield) portion of oil was obtained from 1.84 g of 16a. IR ($CDCl_3$), 1774 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 7.27-6.90 (m, 4 H), 3.28-2.20 (m, 12 H); ^{13}C-NMR ($CDCl_3$), δ, 208.7 (s),

156.1 (s), 133.8 (d), 129.7 (d), 127.5 (s), 120.8 (d), 115.3 (d), 63.8 (t), 63.3 (t), 61.4 (d), 61.0 (d), 50.7 (t), 50.3 (t), 35.9 (t), 35.4 (t), 32.5 (t), 32.3 (t), 31.7 (t), 31.5 (t), 29.3 (d), 29.0 (d).

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.78; H, 7.41. Found: C, 77.88; H, 7.40.

1-Phenylbicyclo[3.2.0]heptan-6-one, 17b. A 68-mg (73 % yield) portion of oil was obtained from 130 mg of 17a by using normal hydrolysis followed by basic hydrolysis. IR ($CDCl_3$), 1778 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 7.35-6.88 (m, 5 H), 3.91-2.69 (m, 3 H), 2.28-1.20 (m, 6 H); ^{13}C-NMR ($CDCl_3$), δ, 212.2 (s), 147.1 (s), 128.4 (d), 126.0 (d), 125.7 (d), 67.0 (d), 57.6 (t), 45.2 (s), 42.6 (t), 30.8 (t), 26.3 (t). GC/MS (70 eV), m/e (relative intensity), 159.0 (2.3), 158.0 (molecular ion - [CO], 18.5), 145.1 (10.9), 144.1 (molecular ion -[H_2C=C=O], 100.0), 129.1 (79.2), 115.1 (39.1).

Anal. Calcd. for $C_{13}H_{14}O$: Mr 186.1045. Found (high-resolution mass spectrometry): M$_r$ 186.1034.

Tricyclo[3.3.3.0^{1,4}]undecan-3-one, 18b. A 322-mg (77 % yield) portion was obtained from 604 mg of 18a by using normal hydrolysis followed by basic hydrolysis: mp 82-83 °C; IR (film), 1774 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 2.49-2.25 (m, 2 H), 2.24-1.07 (m, 12 H), 1.00 (s, 1 H); ^{13}C-NMR ($CDCl_3$), δ, 213.8 (s), 64.4 (d), 63.9 (d), 40.0 (s), 36.3 (t), 36.1 (t), 29.9 (t), 29.5 (t), 28.1 (t), 23.5 (t), 18.9 (t). GC/MS (70 eV), m/e (relative intensity), 164.1 (molecular ion, 11.1), 136.1

(10.4), 121.1 (60.8), 108.0 (64.8), 93.3 (100.0).

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.46; H, 9.65.

Calcd. for $C_{11}H_{16}O$: $\underline{M}_r$ 164.1202. Found (high-resolution mass spectrometry): $\underline{M}_r$ 164.1198.

2-Oxa-3-tetramethylenebicyclo[3.2.0]heptan-7-one, 19b.

A 117-mg (50 % yield) portion of 19b was obtained from 338 mg of 19a as a pale yellow oil: IR (neat), 1786 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 4.10 (m, 1 H), 3.50 (m, 2 H), 2.44-0.92 (m, 11 H); ^{13}C-NMR ($CDCl_3$), δ, 212.1 (s), 96.5 (s), 93.7 (d), 50.0 (t), 42.3 (d), 39.4 (t, 2 C), 31.5 (t), 24.8 (t), 23.7 (t); GC/MS (70 eV), m/e (relative intensity), 139.00 (0.5), 138.10 (molecular ion - [CO], 5.1), 124.00 (molecular ion - [$H_2C{=}C{=}O$], 23.9), 120.10 (10.6), 109.10 (16.0), 95.00 (21.1), 81.00 (23.9), 67.00 (100.00), 55.00 (22.5), 41.00 (39.5), 39.00 (43.0).

Anal. Calcd. for $C_{10}H_{14}O_2$: $\underline{M}_r$ 166.0994. Found (high-resolution mass spectrometry): $\underline{M}_r$ 166.0993.

Intramolecular [2+2] Cycloaddition Reactions of Ketene and Carbonyl Groups. A New Synthesis of Benzofurans

Starting Materials. Salicylaldehyde, 2'-hydroxyacetophenone, 2-hydroxy-3-methoxybenzaldehyde (o-vanillin), 2-hydroxy-4-methoxybenzophenone, 2'-hydroxy-3-phenylpropiophenone, 2-hydroxy-1-naphthaldehyde, and the haloacids were commercially available. 5-Chlorosalicylaldehyde was prepared by a literature procedure (13). 6-Oxo-6-phenylhexanoic acid was prepared previously in this study.

General Procedure for the Preparation of (o-Acylphenoxy)acetic Acids.

Method A. This method utilizes water as a solvent and was used for the preparation of 26a (Table IV, p.86). To a mixture of 8 g (65 mmol) of salicylaldehyde and 7.05 g (65 mmol) of 2-chloropropanoic acid in 20 mL of water was slowly added with cooling and stirring a 20 mL cold aqueous solution containing 6 g (0.15 mol) of NaOH. The mixture was stirred for 20 min and then refluxed overnight. Upon cooling, the solution was washed with three 25-mL portions of chloroform. The aqueous solution was then acidified to pH 1 with dil. HCl and extracted with three 30-mL portions of benzene. The combined benzene extracts were washed with water and brine, dried over anhydrous magnesium sulfate and evaporated in

vacuo to yield the crude acid which was recrystallized from a mixture of hexane and methylene chloride.

Method B. This method utilizes THF as a solvent and was used for the preparation of 24a, 27a, 28a, 29a, 31a, and 32a (Table IV, p.86, 87). To a mixture of equal equivalents * (50 mmol) of o-acylphenol and α-halocarboxylic acid in sufficient amount (100-150 mL) of dry THF was slowly added with effective stirring 2.3 eq of unwashed 60 % NaH in mineral oil. The mixture was stirred for 20 min and then refluxed for 12-24 h. Upon cooling, the reaction mixture was quenched with 180 mL of water and washed with three 40-mL portions of chloroform. The aqueous solution was then acidified to pH 1 with dil. HCl and extracted with three 60-mL portions of benzene. The combined benzene extracts were washed with water and brine, dried over anhydrous magnesium sulfate and evaporated in vacuo to yield the crude (o-acylphenoxy)acetic acid which was recrystallized from a mixture of methylene chloride and hexane. The crude 32a was purified by column chromatography on silica gel (12 % EtOAc-hexane) or by method D.

Method C. This method was identical with method B except a cold sodium o-acylphenolate solution and a cold sodium α-halocarboxylate solution were first separately

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* To simplify the purification, 55 mmol of the corresponding o-acylphenol was used for 24a, 25a, 28a, and 30a.

prepared and then mixed together followed by refluxing. Ketoacids 25a and 30a (Table IV, p.86, 87) were prepared by this method.

Method D. This method was identical with method A, B or C except dicyclohexylammonium salt of the crude acyl acid was prepared which was e asily purified by washing with petroleum ether. A portion of crude 32a was tried with this method. The ammonium salt was suitable directly for the cycloaddition reaction without reconversion to the original acid.

[(o-Formylphenoxy)phenyl]acetic Acid, 24a. A 9.98-g (78 % yield) portion was obtained as a white solid: mp 140-142 °C; IR (DMSO-d6), 3650-2700, 1742, 1665 cm^{-1}; ^{1}H-NMR (DMSO-d6), δ, 10.55 (s, 1 H), 7.67-6.85 (m, 9 H), 5.95 (s, 1 H), ^{13}C-NMR (DMSO-d6), δ, 189.3 (d), 170.5 (s), 159.5 (s), 136.1 (d), 135.7 (s), 128.9 (d), 128.8 (d), 127.9 (d), 127.4 (d), 125.3 (s), 121.7 (d), 114.7 (d), 78.1 (d).

[(o-Acetylphenoxy)phenyl]acetic Acid, 25a. A 6.89-g (51 % yield) portion of 25a was obtained as a white solid: mp 185-187 °C; IR (DMSO-d6), 3700-2930, 1735, 1675 cm^{-1}; ^{1}H-NMR (DMSO-d6), δ, 9.47 (s, 1 H), 7.35-6.46 (m, 9 H), 5.49 (s, 1 H), 2.59 (s, 3 H); ^{13}C-NMR (DMSO-d6), δ, 199.2 (s), 170.5 (s), 156.1 (s), 135.7 (s), 133.5 (d), 129.8 (d), 128.9 (d, s), 128.8 (d), 127.6 (d), 121.2 (d), 113.8 (d), 77.9 (d), 31.8 (q).

2-(o-Formylphenoxy)propanoic Acid, 26a. An 8.83-g (70

% yield) portion of 26a was obtained as a white solid: mp 72-74 °C; IR ($CDCl_3$), 3700-2470, 1755, 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 10.05 (s, 1 H), 7.35-6.38 (m, 4 H), 4.45 (q, J = 6.3 Hz, 1 H), 1.24 (d, J = 6.2 Hz, 3 H); ^{13}C-NMR ($CDCl_3$), δ, 190.7 (d), 174.3 (s), 159.5 (s), 136.0 (d), 128.6 (d), 124.5 (s), 121.3 (d), 113.2 (d), 72.5 (d), 17.7 (q).

2-(2′-Formyl-6′-methoxyphenoxy)butanoic Acid, 27a.

An 8.45-g (71 % yield) portion of 27a was obtained with mp 113-114.4 °C; IR (DMSO-d6), 3700-2850, 1728, 1690 cm^{-1}; ^{1}H-NMR (DMSO-d6), δ, 10.49 (s, 1 H), 6.74-6.31 (m, 3 H), 4.75 (t, 1 H, J = 5.2 Hz), 3.64 (s, 3 H), 1.86 (m, 2 H), 0.98 (t, 3 H, J = 5.6 Hz); ^{13}C-NMR (DMSO-d6), δ, 206.5 (s), 186.8 (s), 163.7 (s), 161.2 (s), 139.4 (d), 132.9 (s), 126.9 (d), 85.1 (d), 58.2 (q), 25.3 (t), 6.8 (q).

[(2′-Benzoyl-5′-methoxyphenoxy)phenyl]acetic Acid, 28a.

A 16.8-g (93 % yield) portion of 28a was obtained with mp 129-131 °C; IR ($CDCl_3$), 3750-2600, 1734, 1665 cm^{-1}); ^{1}H-NMR ($CDCl_3$), δ, 8.73 (s, 1 H), 7.92-6.39 (m, 13 H), 5.47 (s, 1 H), 3.62 (s, 3 H); ^{13}C-NMR ($CDCl_3$), δ, 195.0 (s), 170.2 (s), 162.8 (s), 156.5 (s), 138.2 (s), 134.3 (s), 132.1 (s), 131.7 (d), 129.1 (d), 128.2 (d), 127.6 (d), 127.4 (d), 126.0 (d), 120.9 (d), 105.4 (d), 77.9 (d), 54.7 (q).

(2′-Benzoyl-5′-methoxyphenoxy)acetic Acid, 29a. A 12.2-g (85 % yield) portion of 29a was obtained with mp 110-112 °C; IR (film), 3700-2550, 1742, 1670 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 9.12 (s, 1 H), 7.68-6.24 (m, 8 H), 4.25 (s, 2 H), 3.62 (s,

3 H); ^{13}C-NMR ($CDCl_3$), δ, 195.2 (s), 169.7 (s), 163.3 (s), 158.1 (s), 138.1 (s), 132.6 (d), 132.3 (d), 129.6 (d), 128.4 (d), 128.0 (d), 127.8 (d), 121.1 (s), 105.9 (d), 100.4 (d), 66.0 (t), 55.3 (q).

[o-(3-Phenylpropionyl)phenoxy]phenylacetic Acid, 30a. A 16.4-g (91 % yield) portion of 30a was obtained with mp 115-117 °C; IR ($CDCl_3$), 3700-2600, 1739, 1668 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 10.35 (s, 1 H), 7.64-6.75 (m, 14 H), 5.68 (s, 1 H), 3.53-2.87 (m, 4 H); ^{13}C-NMR ($CDCl_3$), δ, 202.1 (s), 172.3 (s), 155.9 (s), 141.0 (s), 134.5 (s), 134.0 (d), 129.3-122.2 (m), 79.5 (d), 44.2 (t), 30.2 (t).

2-(1′-Formyl-2′-naphthoxy)butanoic Acid, 31a. An 8.39-g (65 % yield) portion was obtained with mp 115-118 °C; IR ($CDCl_3$), 3700-2680, 1732, 1671 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 10.97 (s, 1 H), 9.25 (s, 1 H), 7.79-6.88 (m, 6 H), 4.91 (t, 1 H, J = 6.3 Hz), 2.12 (m, 2 H), 1.15 (t, 3 H, J = 7.0 Hz); ^{13}C-NMR ($CDCl_3$), δ, 193.3 (d), 174.9 (s), 161.9 (s), 139.2 (s), 137.7 (s), 131.5-113.6 (m), 78.3 (d), 26.0 (t), 9.4 (q).

2-(2′-Formyl-4′-chlorophenoxy)hexanoic Acid, 32a. A 10.28-g (76 % yield) portion was obtained as a colorless oil: IR (neat), 3650-2180, 1738, 1685 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 11.08 (s, 1 H), 10.42 (s, 1 H), 7.53 (s, 1 H), 7.21 (d, 1 H, J = 8.2 Hz), 6.83 (d, 1 H, J = 8.2 Hz), 4.62 (t, 1 H, J = 5.6 Hz), 2.25-0.74 (m, 9 H); ^{13}C-NMR ($CDCl_3$), δ, 188.6 (d), 174.6 (s) 158.6 (s), 135.0 (d), 127.7 (d), 126.8 (s), 126.2 (s), 114.8 (d), 53.5 (d), 32.0 (t), 27.1 (t), 24.1 (t), 13.5 (q).

Dicyclohexylammonium 2-(2'-Formyl-4'-chlorophenoxy)-hexanoate, 33a. A pale yellow dicyclohexylammonium salt was obtained from a portion of crude 32a: mp 183-184 °; IR (film), 3280-2150, 1678, 1639 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 10.51 (s, 1 H), 7.77 (s, 1 H), 7.38-6.84 (m, 2 H), 4.46 (t, J = 6.2 Hz, 1 H), 2.63 (m, 2 H), 2.07-0.84 (m, 31 H); ^{13}C-NMR ($CDCl_3$), δ, 188.7 (d), 174.5 (s), 160.1 (s), 134.6 (d), 126.9 (d), 125.5 (s), 125.4 (s), 115.4 (d), 79.8 (d), 52.2 (d), 32.9 (t), 28.8 (t), 28.1 (t), 25.1 (t), 24.6 (t), 22.6 (t), 14.0 (q).

General Procedure for Intramolecular Cycloadditions of Ketenes to Carbonyl Groups.

Method A. This method was similar to the previously described Method A for the intramolecular cycloadditions of phenoxyketenes to carbon-carbon double bonds except the reactions of acyl acids with oxalyl chloride took a longer time (4-8 h). During the cycloadditions carbon dioxide was evolved and could be trapped as carbonate by using aqueous calcium oxide. Benzofurans 24b, 25b, 26b, 27b, 28b, and 29b (Table IV, p.86) were prepared by this method.

Method B. This method was identical with the previously described Method B for the intramolecular cycloadditions of phenoxyketenes to carbon-carbon double bonds. Benzofurans 24b, 28b, 30b, 31b, and 32b (Table IV, p.86, 87) were prepared by this method.

Method C. This method was identical with Method B

except the washed dicyclohexylammonium salts were used instead of the free acyl acids. Benzofuran 32b was also prepared by this method.

2-Phenylbenzofuran, 24b. A 0.85-g (75 % yield) portion and a 0.87-g (78 % yield) portion of 24b were obtained as white crystals from 1.5 g of 24a by Methods A and B, respectively. The mp (120-121 °C) and spectra were identical with those in the literature (14, 15).

3-Methyl-2-phenylbenzofuran, 25b. A 1.32-g (78 % yield) portion was obtained from 2.2 g of 25a as white solid. The mp (34-34.5 °C) and spectra were identical with those in the literature (16, 17, 18, 19).

2-Methylbenzofuran, 26b. A 0.97-g (57 % yield) portion of 26a as a colorless oil was obtained from 2.5 g of 26a. The spectra were identical with those in the literature (20).

2-Ethyl-7-methoxybenzofuran, 27b. A 0.98-g (53 % yield) portion of 27b as a colorless oil was obtained from 2.5 g of 27a. IR (neat), 1625 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 6.92-6.05 (m, 4 H), 3.72 (s, 3 H), 2.61 (q, 2 H, J = 7.5 Hz), 1.57 (t, 3 H, J = 7.5 Hz); ^{13}C-NMR ($CDCl_3$), δ, 160.8 (s), 144.8 (s), 142.6 (s), 130.5 (s), 122.8 (d), 112.6 (d), 105.4 (d), 101.1 (d), 55.6 (q), 21.5 (t), 11.7 (q).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.81; H, 6.92.

6-Methoxy-2,3-diphenylbenzofuran, 28b. A 1.36-g (82 % yield) portion and a 1.39-g (84 % yield) portion of 28b were

obtained from 2 g of 28a by Methods A and B, respectively, with mp 120-121 °C; IR (film), 1614 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 7.89-6.68 (m, 13 H), 3.71 (s, 3 H); ^{13}C-NMR ($CDCl_3$), δ, 158.4 (s), 154.9 (s), 149.5 (s), 132.9 (s), 130.8 (s), 129.6-126.5 (m), 123.6 (d), 120.1 (d), 117.4 (d), 111.8 (d), 55.5 (q).

Anal. Calcd. for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37. Found: C, 84.09; H, 5.34.

6-Methoxy-3-phenylbenzofuran, 29b. A 1.28-g (74 % yield) portion was obtained from 2.2 g of 29a with mp 43-44 °C; IR ($CDCl_3$), 1624 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 7.74-6.70 (m, 9 H), 3.68 (s, 3 H); ^{13}C-NMR ($CDCl_3$), δ, 158.1 (s), 156.8 (s), 140.1 (d), 132.1 (s), 128.8 (d), 127.1 (d), 121.9 (s), 120.4 (d), 119.6 (s), 112.0 (d), 96.1 (d), 55.3 (q).

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.32; H, 5.40. Found: C, 79.96; H, 5.43.

2-Phenyl-3-(2'-phenylethyl)benzofuran, 30b. A 1.47-g (89 % yield) portion was obtained as a colorless oil from 2 g of 30a. IR (neat), 1622 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 7.62-6.85 (m, 14 H), 3.28-2.80 (m, 4 H); ^{13}C-NMR ($CDCl_3$), δ, 154.0 (s), 151.1 (s), 141.3 (s), 131.1 (s), 130.3 (s), 128.5 (d), 128.4 (d), 128.0 (d), 126.8 (d), 126.1 (d), 124.3 (d), 122.3 (d), 119.5 (d), 115.3 (s), 111.0 (d), 35.6 (t), 26.3 (t).

Anal. Calcd. for $C_{22}H_{18}O$: C, 88.56; H, 6.08. Found: C, 88.34; H, 6.13.

2-Ethylnaphtho[2,1-b]furan, 31b. A 1.24-g (74 % yield) portion was obtained as a colorless oil from 2.2 g of 31a.

IR (neat), 1632 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 8.38-7.51 (m, 6 H), 7.13 (s, 1 H), 3.17 (q, 2 H, J = 7.6 Hz), 1.64 (t, 3 H, J = 7.6 Hz); ^{13}C-NMR ($CDCl_3$), δ, 160.2 (s), 151.9 (s), 130.3 (s), 128.6 (d), 125.8-123.8 (m), 112.1 (d), 100.1 (d), 21.9 (t), 12.1 (q).

Anal. Calcd. for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.58; H, 5.91.

2-n-Butyl-5-chlorobenzofuran, 32b. A 1.29-g (72 % yield) portion and a 0.63-g (70 % yield) portion were obtained as colorless oils from 2.4 g of 32a (Method B) and 2.0 g of 33a (Method C), respectively. IR (neat), 1613 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 7.24-6.78 (m, 3 H), 6.02 (s, 1 H), 2.87-0.68 (m, 9 H); ^{13}C-NMR ($CDCl_3$), δ, 161.3 (s), 153.0 (s), 130.5 (s), 127.9 (s), 123.1 (d), 119.7 (d), 111.4 (d), 101.4 (d), 29.6 (t), 28.1 (t), 22.2 (t), 13.7 (q).

Anal. Calcd. for $C_{12}H_{13}OCl$: C, 69.07; H, 6.28. Found: C, 68.94; H, 6.10.

Demonstration of the Intermediacy of Phenoxyketenes in the Benzofuran Synthesis.

7-(2'-Formylphenoxy)-7-phenylbicyclo[3.2.0]hept-2-en-6-one, 24c. A solution of 2.53 g (25 mmol) of triethylamine in 10 mL of dry benzene was added dropwise with stirring to a solution containing 13.2 g (0.2 mol) of fresh cyclopentadiene and a crude (2-formylphenoxy)phenylacetyl chloride (prepared from 5.12 g, 20 mmol, of 24a) in 50 mL of benzene

at ice temperature. After 3 h of stirring with an ice bath the reaction mixture was allowed to warm up to room temperature and stirred for an additional 6 h. The salt was filtered and the filtrate evaporated. A column chromatography on silica gel afforded 2.74 g (45 % yield) of 24c as a pale yellow oil: IR (neat), 1783, 1687 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ, 10.32 (s, 1 H), 7.72-6.63 (m, 9 H), 5.96-5.50 (m, 2 H), 4.28-3.49 (m, 2 H), 2.80-2.28 (m, 2 H); ^{13}C-NMR ($CDCl_3$), δ, 208.7 (s), 189.5 (d), 158.0 (s), 135.9 -124.1 (m), 121.7 (d), 117.5 (d), 98.9 (s), 59.7 (d), 51.2 (d), 34.5 (t), 13.4 (q).

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CHAPTER III

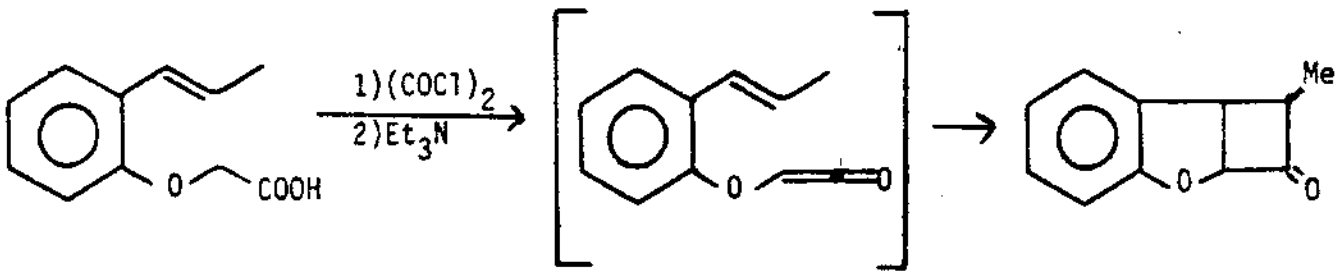
RESULTS AND DISCUSSION

Intramolecular [2+2] Cycloadditions of Phenoxyketenes to Carbon-Carbon Double Bonds

(o-Alkenylphenoxy)acetic acids were initially chosen as precursors to the difunctional compounds needed for the intramolecular [2+2] ketene-olefin cycloadditions. These acids provided the most favorable proximity for the cycloaddition reactions and were readily prepared from commercially available or easily made o-alkenylphenols and α-halocarboxylic acids as illustrated for (o-propenylphenoxy)acetic acid. A solution of sodium α-bromo- or chlorocarboxylate

and sodium o-alkenylphenolate in THF or water was refluxed for 4-16 h. Yields of 50-88% were obtained after recrystallization from hexane or water.

The (o-alkenylphenoxy)acetic acids were converted to the corresponding acid chlorides by reaction with an excess of oxalyl chloride * in benzene at ambient temperature for 3 h. The excess oxalyl chloride was removed under vacuum and the crude acid chloride diluted with benzene and slowly added to a solution of 2-3 equivalents of triethylamine in benzene at gentle reflux. This dehydrochlorination resulted in the phenoxyketene which underwent the [2+2] cycloaddition with the carbon-carbon double bond in the ortho position as illustrated with (o-propenylphenoxy)acetic acid. The cyclo-



addition products were purified by column chromatography (3-7% EtOAc-hexane) or recrystallization from hexane. In the above scheme the intramolecular [2+2] cycloaddition reaction occurs with the simultaneous formation of a five-membered ring, i.e., the ketene functionality and the double bond are separated by a bridge of three atoms. These cycloadditions

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* Oxalyl chloride gives a cleaner reaction and is easier to handle than thionyl chloride.

occurred in yields of 43-88% and the results are tabulated in Table I. The structures of the cycloaddition products were determined by the presence of the carbonyl band in the infrared spectra at 1777-1789 cm^{-1}, the ^{1}H- and ^{13}C-NMR spectra and elemental analysis.

To reduce the probability of dimerization or intermolecular cycloaddition, it is necessary to keep a low concentration of the reacting ketene. This is accomplished by the slow addition of a dilute solution of the acid chloride to a dilute solution of triethylamine.

It is very interesting to note that these intramolecular [2+2] cycloadditions are quite stereoselective. We were unable to assign all stereoisomers based solely on the NMR spectra due to the complexity of the compounds and the limited resolution of the spectra. However, a comparison of the abundances and fragmentation patterns of the isomers in the GC/MS spectra of all the cycloaddition products strongly suggested that one of the possible stereoisomers always predominated in a cycloaddition reaction. As illustrated with entry 8, there were obtained two diastereomeric pairs of enantiomers resulting from two chiral centers. The ratio of the two pairs was about 5 : 1. These results were similar to those from the intermolecular [2+2] cycloadditions of ketenes to olefins and suggested a concerted $[\pi_a 2 + \pi_s 2]$ mechanism with a little leading bond formation between the sp-hybridized carbon of the ketene and the less substituted end of the

Table I. Intramolecular [2+2] Cycloadditions of Phenoxyketenes Derived from (o-Alkenylphenoxy)acetic Acids

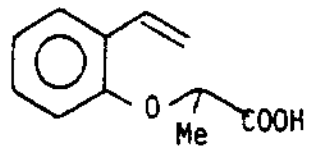
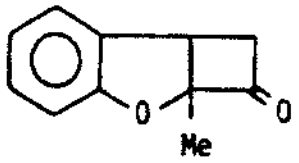
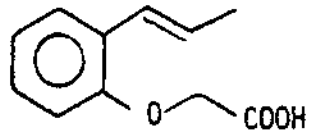
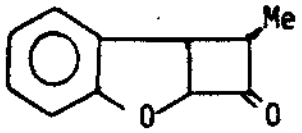
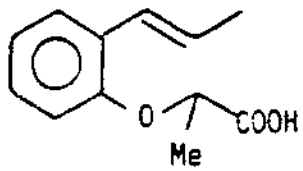
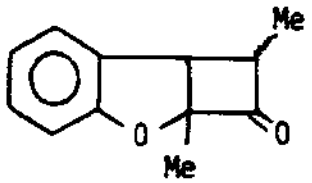
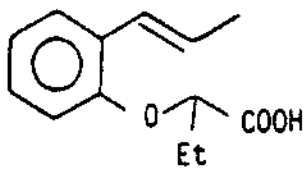
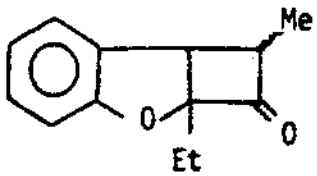
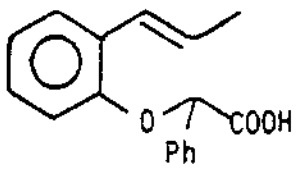
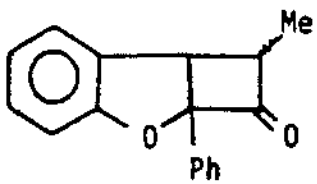
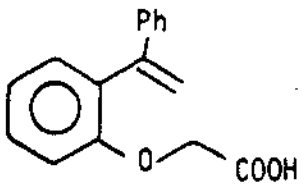
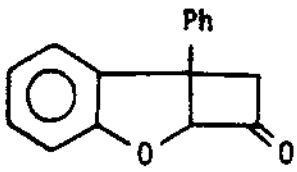
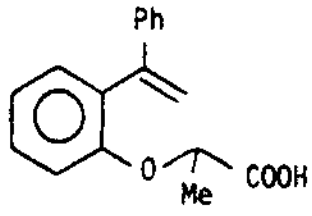
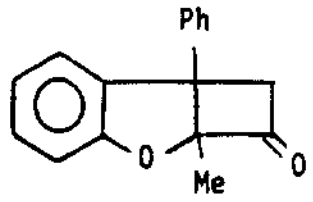
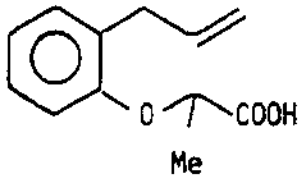
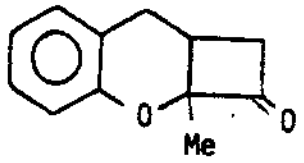
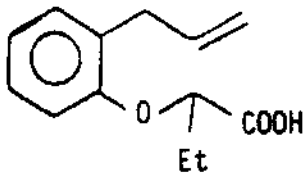
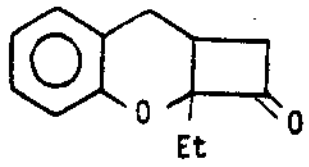
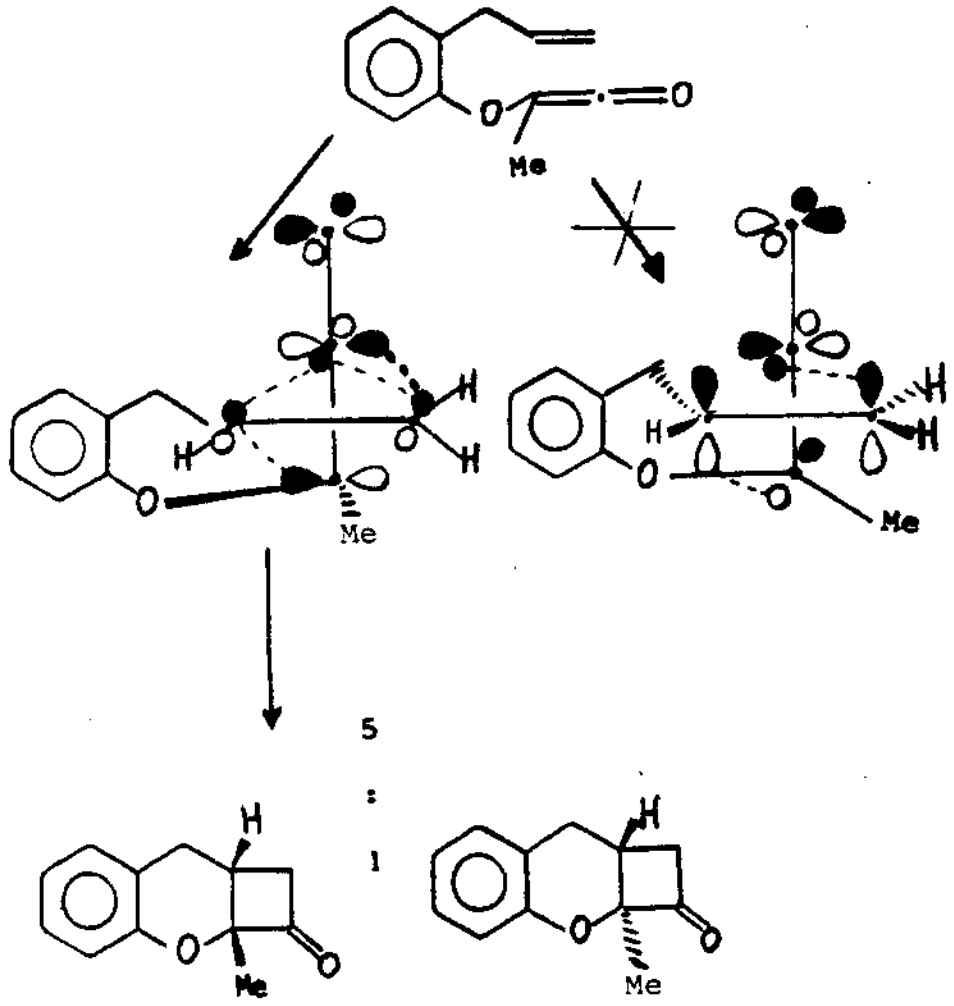
Entry	Acid, a	Cycloadduct, b	Yield (%)
1			60
2			72
3			76
4			71
5			85
6			88

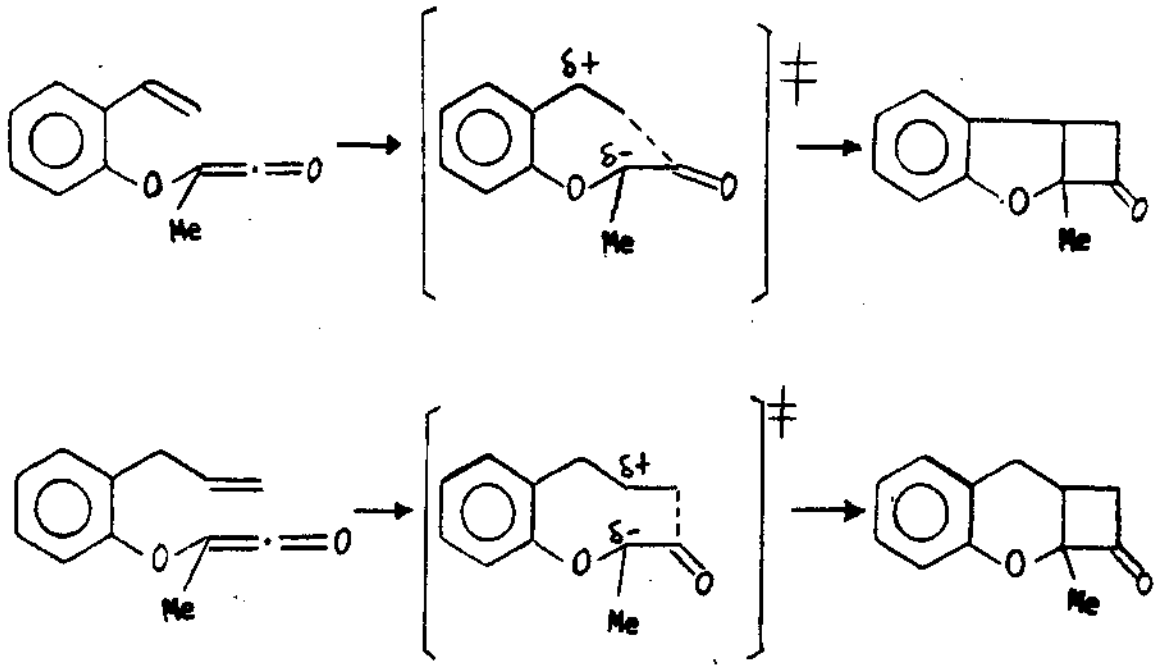
Table I. Continued

Entry	Acid, a	Cycloadduct, b	Yield (%)
7			84
8			43
9			49



carbon-carbon double bond in the transition state for the intramolecular counterparts (1, 2, 3, 4, 5, 6, 7, 8, 9, 10).

The (o-vinylphenoxy)ketenes clearly give much better yields of the intramolecular [2+2] cycloaddition products than the (o-allylphenoxy)ketenes as revealed in Table I. This is probably due to the greater reactivity of (o-vinylphenoxy)ketenes because in the initial bond formation between the sp-hybridized carbon atom of the ketene and the carbon-carbon double bond any positive charge developed in the transition state is on a benzylic carbon atom.

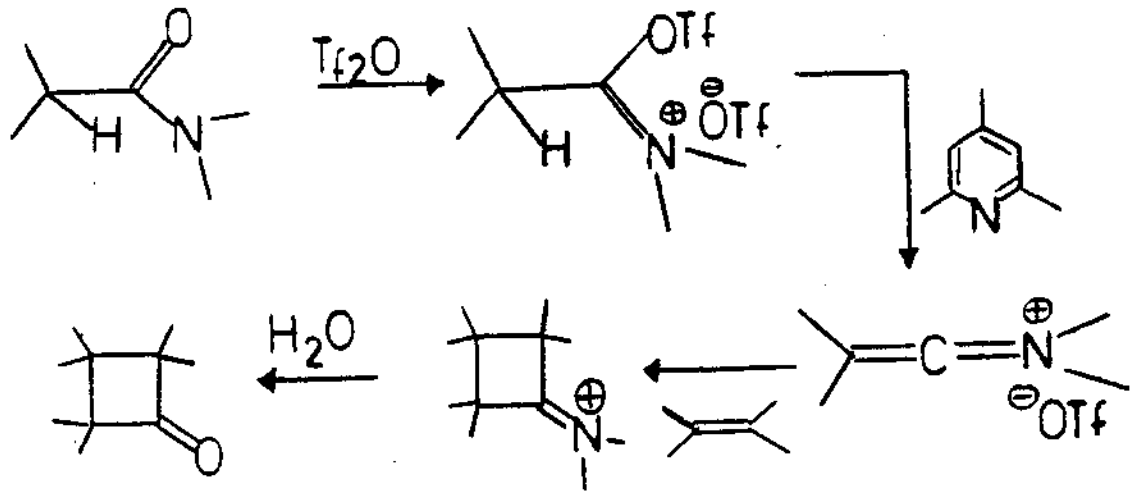


Substitution in the (o-alkenylphenoxy)acetic acids at the position α to the carboxyl group (acids that would lead to disubstituted ketenes) does not provide any steric problems for the cycloaddition as evidenced by entries 1, 3, 4, 5, and 7. Also, substitution of a methyl or phenyl group on the vinyl substituent as in entries 2-7 provides no difficulties for the cycloaddition.

This study clearly indicates the usefulness of intramolecular [2+2] cycloaddition reactions of ketenes which promises to be a powerful synthetic tool for the synthesis of a wide variety of polycyclic compounds.

Intramolecular [2+2] Cycloadditions of Keteniminium Salts to Carbon-Carbon Double Bonds

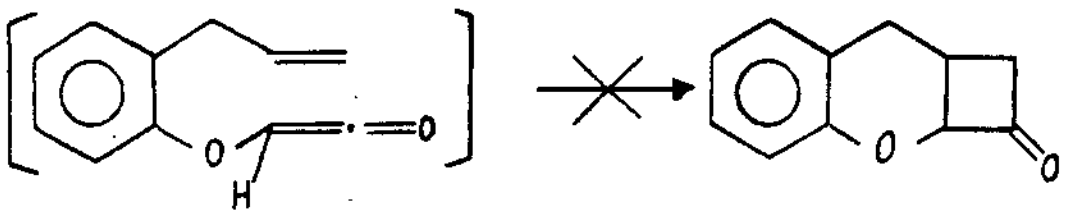
The intermolecular [2+2] cycloaddition reaction of keteniminium salts was developed by Ghosez and coworkers (11). Treatment of an appropriate amide with 1 equivalent of trifluoromethanesulfonic anhydride (triflic anhydride, Tf_2O) and 1 equivalent of collidine by the procedure of Ghosez et al. gives a keteniminium salt that can add to a carbon-carbon double bond to give, after hydrolysis, a cyclobutanone.



Keteniminium salts are more electrophilic than ketenes and will react with less nucleophilic olefins and do not undergo dimerization and oligomerization like many ketenes, particularly aldoketenes. Therefore, since both ketenes and keteniminium salts are readily obtained from the same acid halide, the intramolecular cycloaddition of keteniminium

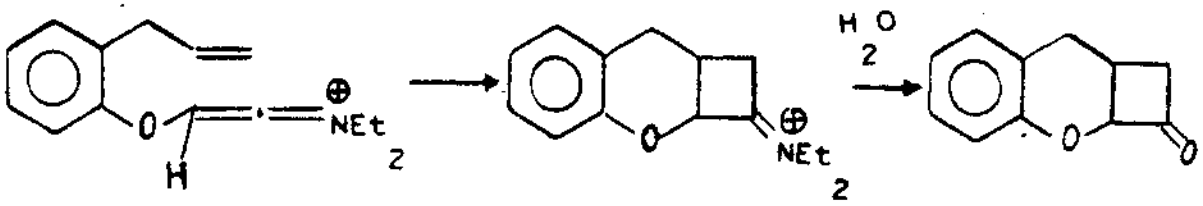
salts should complement ketene cycloadditions. However, the use of keteniminium salts instead of ketenes in intramolecular cycloadditions does have some limitations. This study describes the intramolecular [2+2] cycloaddition of keteniminium salts with carbon-carbon double bonds and compares these cycloadditions with the corresponding ketene cycloadditions. During the course of this dissertation study, two communications and one full paper appeared in the literature on intramolecular [2+2] cycloadditions of keteniminium salts to carbon-carbon double bonds (12, 13, 14).

We have attempted the intramolecular [2+2] cycloaddition of (o-allylphenoxy)ketene (an aldoketene connected to an unreactive carbon-carbon double bond) many times under a variety of reaction conditions but have not been able to isolate the cycloaddition product. It is well known that



aldoketenes are unstable and susceptible to dimerization and oligomerization and evidence suggests that this was the fate of the aldoketene in this reaction. Conversely, the intramolecular [2+2] cycloaddition of the corresponding (o-allyl-

phenoxy)keteniminium salt occurred in a 44% yield (entry 13



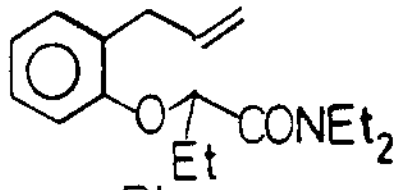
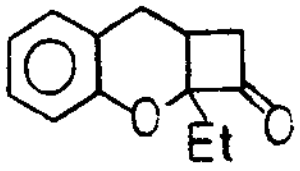
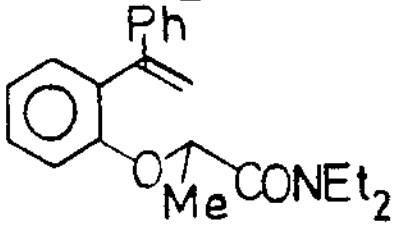
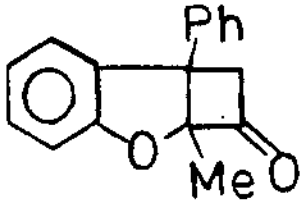
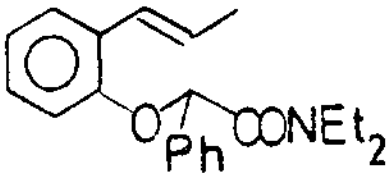
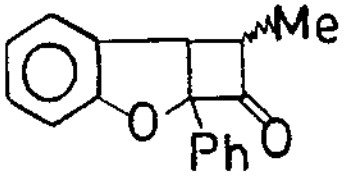
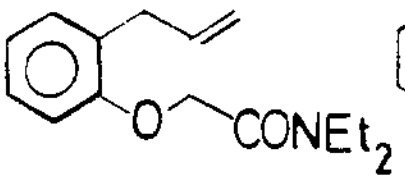
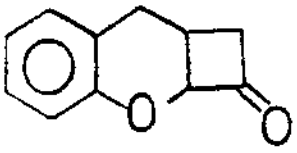
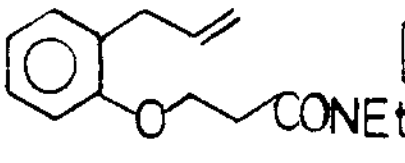
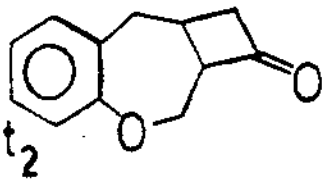
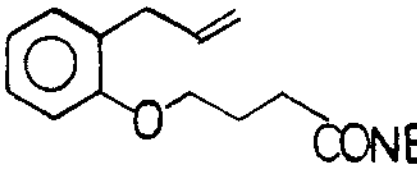
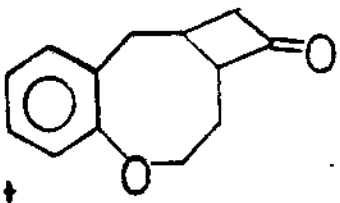
44 %

in Table II). The inability of the keteniminium salt to dimerize and the greater reactivity with the less nucleophilic carbon-carbon double bond is apparently responsible for this cycloaddition.

An examination of the results presented in Table II clearly shows that for ketoketenes the ketene cycloaddition process provides better yields than the keteniminium salt method as indicated by entries 10-12. However, the aldoketenes in Table II give much poorer yields than the keteniminium salt method as illustrated with entries 13-19. This difference is very dramatic with entries 17-19. However, it should be noted that entries 17-18 are not alkoxyketenes or alkoxyketeniminium salts but rather just alkylaldoketenes which are less reactive than alkoxyketenes.

Increasing the bridge between the keteniminium salt function and the carbon-carbon double bond from 3 to 7 atoms (entries 12-16) results in a significant reduction in yield. However, this is not believed to be due to the increased

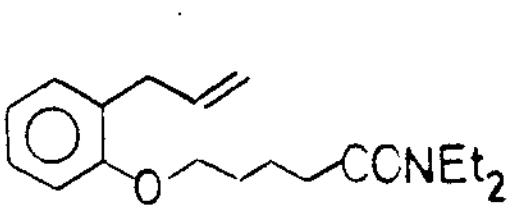
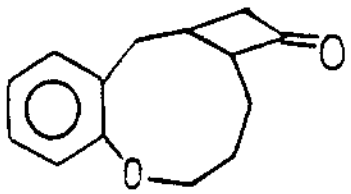
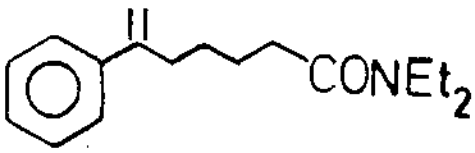
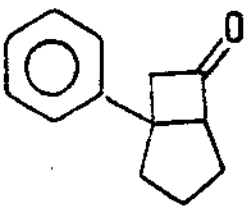
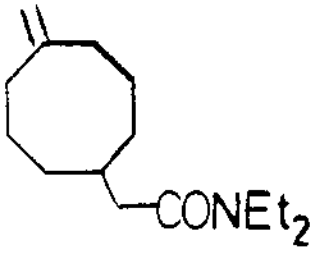
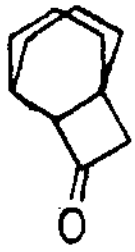
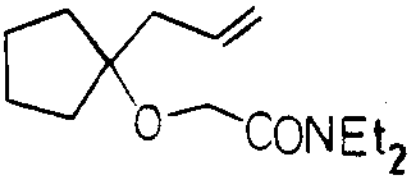
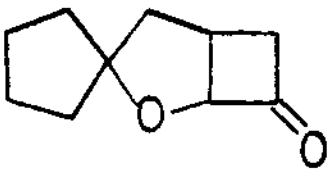
Table II. Intramolecular [2+2] Cycloadditions of Keteniminium Salts

Entry	Amide, a	Cyclobutanone, b*	Yield (%)**	
10			32	49
11			70	84
12			66	85
13			44	0
14			18	0
15			10	0

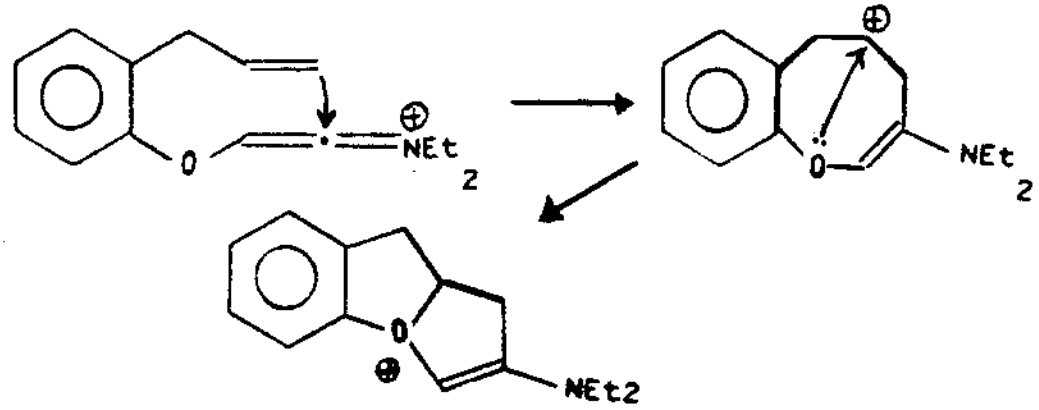
* 10b=9b, 11b=7b, 12b=5b; see Table I, p.65, 66.

** The underlined yields are those obtained by the corresponding ketene cycloadditions.

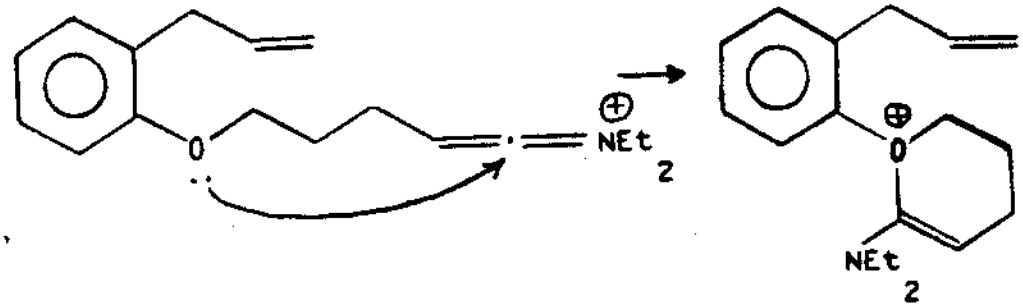
Table II. Continued

Entry	Amide, a	Cyclobutanone, b	Yield (%)	
16			4	—
17			73	12
18			77	0
19			50	—

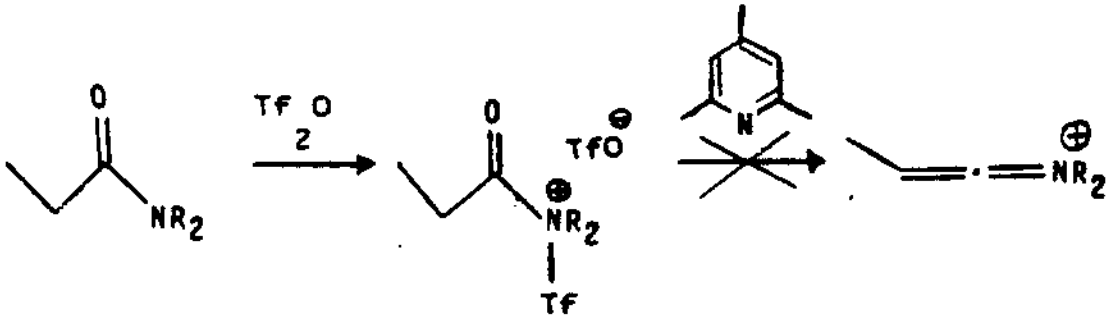
bridge but rather the ability of the nucleophilic oxygen atom to become involved in the reaction as has been previously shown. Since the [2+2] cycloaddition of keteniminium salts to the carbon-carbon double bond likely proceeds via a stepwise mechanism (14), the oxygen atom of the ether linkage of the alkenyloxyketeniminium salt may undergo a nucleophilic attack on the positive-charged carbon in the initially formed intermediate to generate an oxonium salt if the bridge between the two reacting functional groups is no less than four atoms.



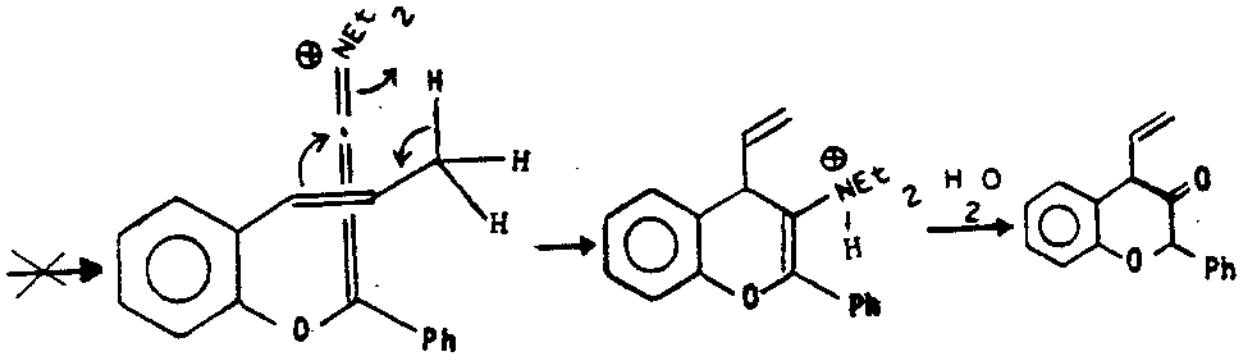
Entries 15 and 16 also provide another possibility for a facile cyclization without involvement in the olefin function as illustrated with entry 16.



Although the size of the keteniminium salt function may provide steric hindrance to the cycloaddition, the cycloadditions of entries 10-12 gave good yields. The generally low yields for the keteniminium salt cycloaddition may be largely attributed to the intrinsic formation of N-acylated side products which cannot give rise to the keteniminium salt in the presence of collidine.



Probably due to steric hindrance, the cycloaddition of entry 12 did not have much competing ene reaction which would usually yield the Friedel-Crafts adduct upon hydrolysis as illustrated.



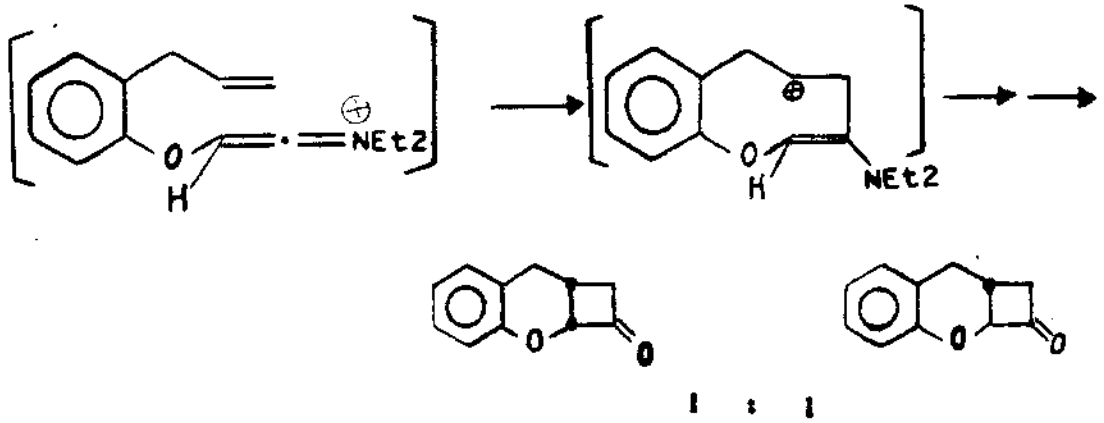
The comparison of the intramolecular ketene and keteniminium salt procedures in entry 17 is particularly note-

worthy. This is an example of an aldoketene or aldoketeniminium salt separated by a three atom bridge and the keteniminium salt gives a 73 % yield and the ketene procedure gives only a 12 % yield. Also, in entry 18 the keteniminium salt procedure gives a 77 % yield of the adduct and the ketene gave no detectable cycloaddition product.

Despite the low yields, the products of entries 13-16 have not been available by any conventional method. The cycloadduct obtained from entry 18 is a very interesting polycyclic compound and the cycloaddition of the keteniminium salt of amide 19a provides a new approach to spiro compounds.

The hydrolysis of the initially formed cycloadduct, an iminium salt, for entries 17 and 18 could only be accomplished by an alkaline aqueous solution. However, these basic hydrolysis conditions would destroy 19b even at ambient temperature.

Unlike the stereoselective intramolecular [2+2] ketene-olefin cycloadditions, the intramolecular [2+2] keteniminium salt-olefin cycloadditions gave different mixtures of stereo-

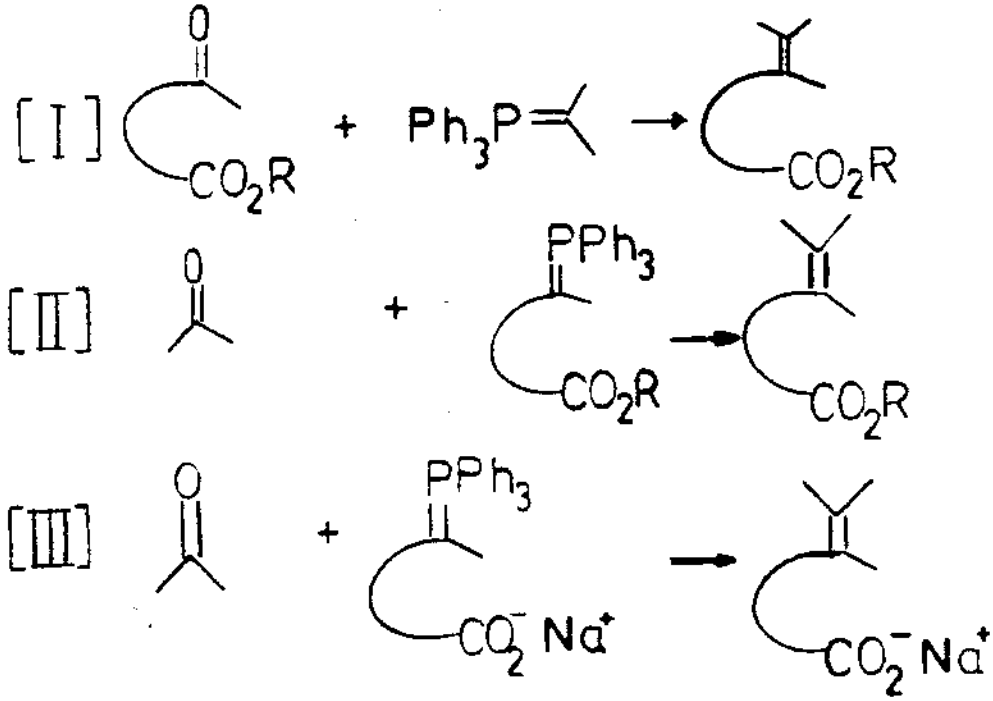


1 : 1

isomers because of the change from a concerted to a stepwise mechanism as illustrated with entry 13.

During the course of this study, a convenient method for the synthesis of precursors for intramolecular cycloadditions of ketenes to carbon-carbon double bonds was discovered as a collaboration effort with Wu (15). That is, the Wittig Reaction of ketoacids without protecting the carboxyl groups to yield alkenoic acids.

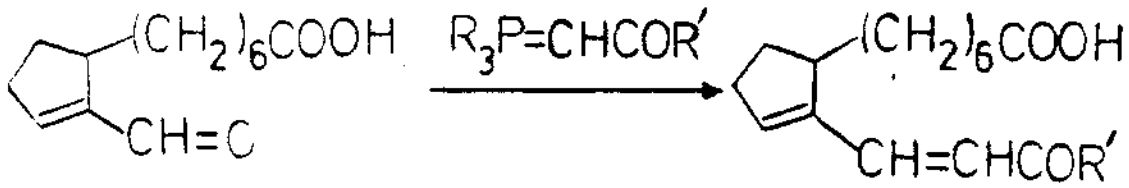
In a literature search for the preparation of suitable unsaturated acids, the precursors needed for the intramolecular ketene- or keteniminium salt-olefin cycloadditions, we found only a few reports. Most of these reports utilized the conventional Wittig Reaction. There are generally three types of Wittig Reactions most often found in the literature.



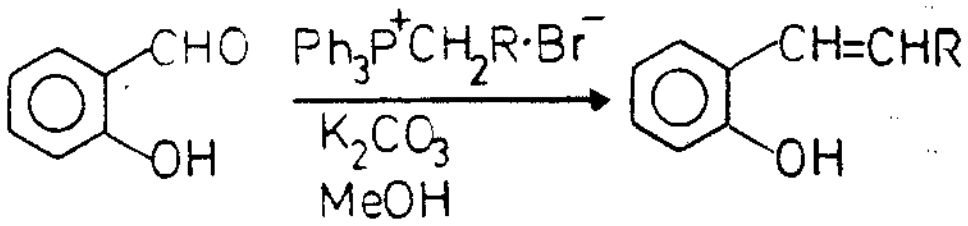
Routes [I] (16, 17, 18) and [II] (19, 20, 21, 22) require esterification of the ketoacid and then removal of this protecting group, which considerably reduces the efficiency of the reaction. In route [III] (23, 24, 25), the starting haloacids in which the halogen atoms are not in the α-position are relatively unavailable.

The direct conversion of readily available ketoacids to unsaturated acids in one step without protecting the carboxyl groups by using an excess of the Wittig reagent was accomplished in this study.

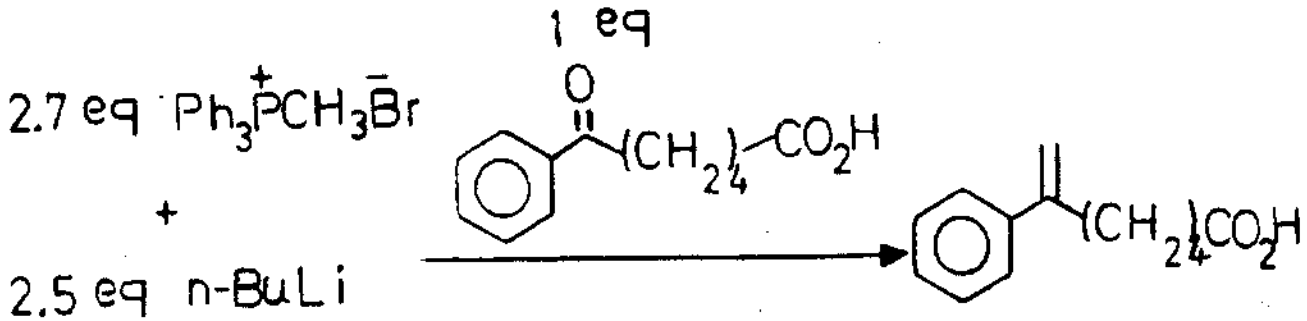
The only available report on such a procedure in the literature was a Japanese Patent which describes the synthesis of a prostaglandin-related compound (26).



The Wittig Reaction of salicylaldehyde without protecting the hydroxyl group (27) prompted the exploration of this procedure.



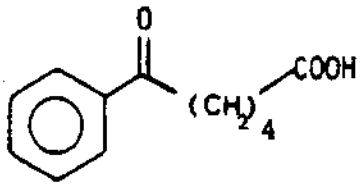
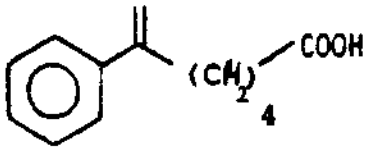
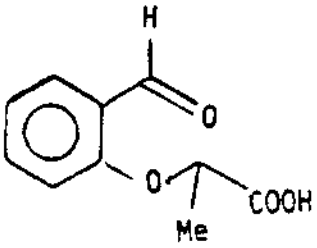
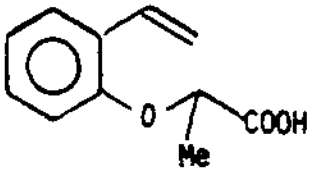
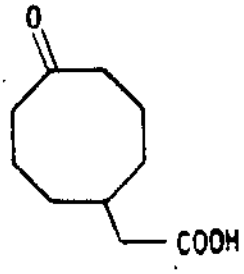
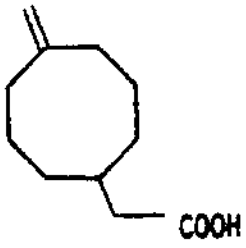
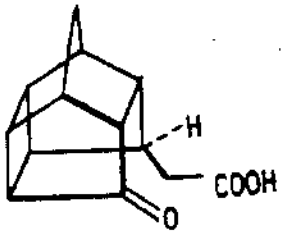
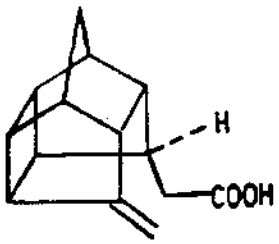
The Wittig Reaction of ketoacids proceeds readily and smoothly with an excess of the reagent and usually will take place at ambient temperature or lower than 60 °C as illustrated with the preparation of 6-phenyl-6-heptenoic acid.



The starting ketoacids are usually quite accessible and it was for this reason the one-step Wittig Reaction was the most reliable source of alkenoic acids. The conversion of four ketoacids to unsaturated acids along with yields are shown in Table III. Ketoacid 20c was prepared by a standard procedure for ketoacids (28, 29) and 21c was easily prepared from salicylaldehyde and 2-chloropropanoic acid. The ethyl esters of 22c and 23c were provided by Wu (15).

Entries 20, 22, and 23 are all new compounds which would likely be difficult to prepare by other methods. For instance, the application of the Peterson Reaction (30, 31, 32, 33) and the Grignard Reaction to the syntheses of 22d and

Table III. Conversion of Ketoacids to Unsaturated Acids by Wittig Reaction

Entry	Ketoacid, c	Unsaturated Acid, d *	Yield (%)
20			71
21			56
22			79
23			82

* 21c = 26a in Table IV, p.86; 21d = 1a in Table I, p.65.

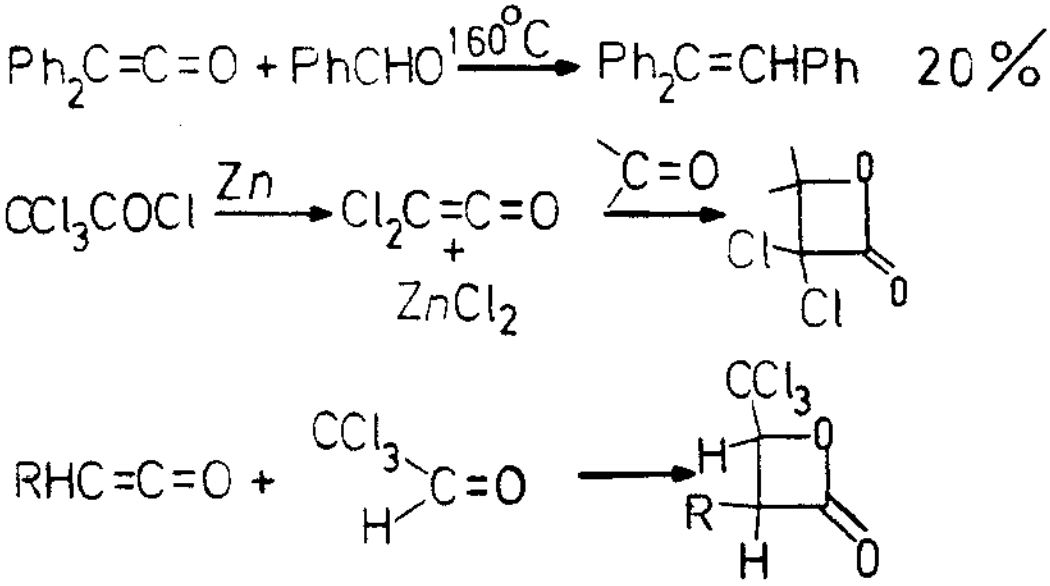
23d have been unsuccessful either with or without protecting the carboxyl groups. Although 21d (= 1a in Table I, p.65) has been prepared from o-vinylphenol and 2-halopropanoic acid previously, the instability of o-vinylphenol has made the preparation very difficult.

Table III shows that both aldehydes and ketones, either with or without a ether linkage, will undergo this convenient reaction in satisfactory yields and usually the alkenoic acids are sufficiently pure for the direct use in the cyclo-additions. Although this reaction requires more than two equivalents of the corresponding ylide, this procedure is still more efficient than the carboxyl-protected route because it essentially eliminates two steps and also provides much easier purification.

It is proposed that the conditions suitable for this reaction will generally parallel those for ordinary Wittig Reactions. The following bases and solvents have been successfully utilized in this procedure: dry n-BuLi/DMSO, NaH/DMSO, NaH/THF, NaH/DMF.

Intramolecular [2+2] Cycloaddition Reactions of Ketene and Carbonyl Groups. A New Synthesis of Benzofurans

The intermolecular cycloaddition of ketenes to carbonyl compounds is significantly different from the cycloaddition to olefinic compounds. Elevated temperatures, Lewis Acid catalysts or activation of the carbonyl group is usually required for intermolecular ketene-carbonyl compound cycloadditions (34, 35, 36, 37, 38, 39). However, in an appro-

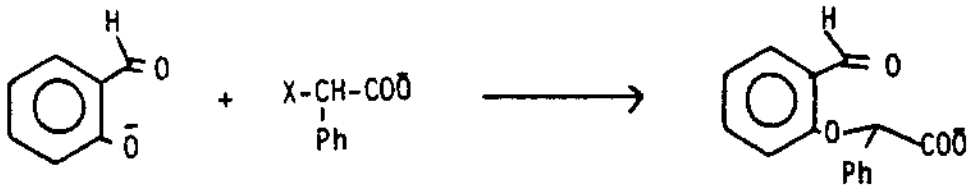


priate intramolecular cycloaddition of a ketene function with a carbonyl group the proximity of the two functional groups provides a more favorable condition for cycloaddition. We found that the cycloadditions occur readily with both aldehydic and ketone carbonyl groups.

The difunctional compounds used as precursors for the intramolecular cycloadditions were (o-acylphenoxy)acetic

acids. The reason for this choice was threefold. First, these acids can be readily prepared from commercially available or easily made o-acylphenols and α-halocarboxylic acids. Second, the proxmity of the two functional groups, the high-lying HOMO (raised by conjugation with the benzene ring) of the carbonyl group (40), and the aromaticity of the anticipated product (benzofuran) were all expected to provide most favorable conditions for cycloaddition. Third, the convenient synthesis of benzofurans by the decarboxylation of the cycloaddition products should in many cases serve as a much improved procedure for the preparation of many substituted benzofurans.

As illustrated for (o-formylphenoxy)phenylacetic acid, equal molar amount * of salicylaldehyde and α-bromophenylacetic acid in dry THF upon treatment with sodium hydride and refluxing gave a 78% yield of the desired difunctional compound. Yields of 51-93 % of the (o-acylphenoxy)acetic acids



* See page 51.

were obtained after recrystallization from a mixture of hexane and methylene chloride.

The ketenes were generated from either the acid chlorides or acyl tosylates. The conversion of appropriate acyl tosylates to ketenes is a new procedure and will be discussed in the next section.

The (o-acylphenoxy)acetic acids were converted to the corresponding acid chloride by reaction with 5-8 equivalents of oxalyl chloride * in benzene at ambient temperature for 4-8 h. The excess oxalyl chloride was removed under vacuum and the crude acid chloride diluted with dry benzene and very slowly added to a dilute solution of 3 equiv of triethylamine in benzene at reflux. The dehydrochlorination of the acid chloride was evident by the immediate formation of the amine salt. The reaction mixture was refluxed for up to 3-4 h during which time carbon dioxide was evolved as evidenced by trapping as the carbonate. We believe this dehydrochlorination resulted in the phenoxyketene which underwent a [2+2] cycloaddition reaction with the carbonyl group in the ortho position to yield the β-lactone as illustrated with (o-formylphenoxy)phenylacetic acid.

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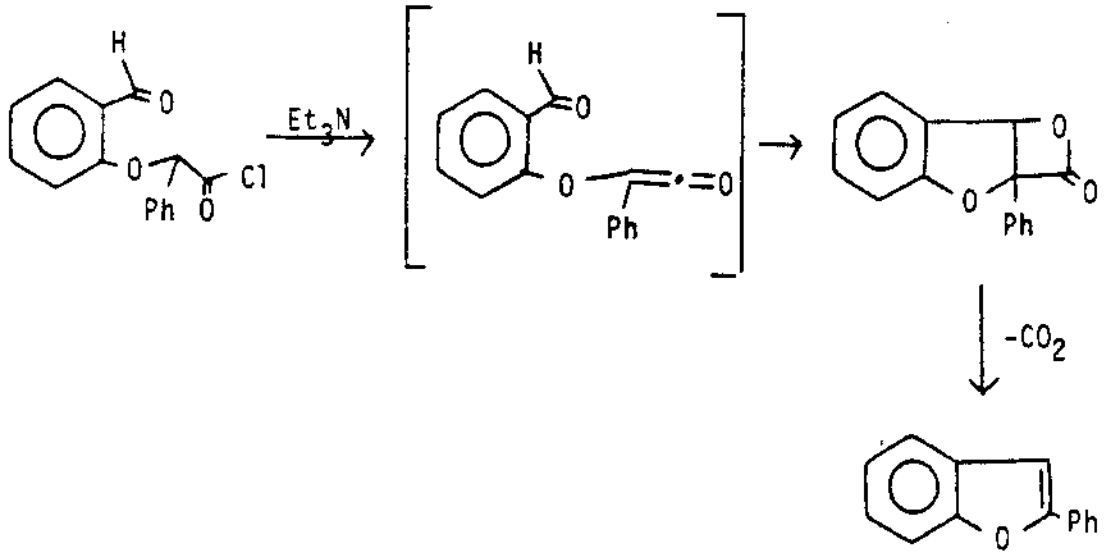
* The use of thionyl chloride instead of oxalyl chloride may cause an attack on the carbonyl group (41). Also, oxalyl chloride gives a cleaner reaction.



The tricyclic β-lactone cycloaddition product spontaneously underwent decarboxylation to yield the benzofuran as evidenced by the elimination of carbon dioxide. The workup simply involved filtration to remove the amine salt and purification by use of a silica gel column (hexane or 0.5 % ethyl acetate in hexane). Pure benzofurans were obtained in yields of 53-82 % * from the corresponding carboxylic acids as illustrated in Table IV. Refluxing benzene or toluene may be used as the solvent for the cycloaddition.

It is of interest to note in Table IV that unlike <u>inter</u>molecular cycloadditions, there is little difference in

* These yields are only refered to those from the acid chloride method.

Table IV. The Synthesis of Benzofurans via Intramolecular [2+2] Cycloadditions of (o-Acylphenoxy)ketenes

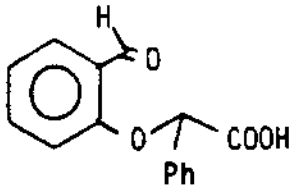
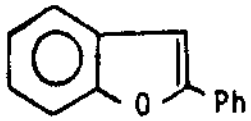
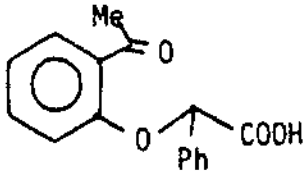
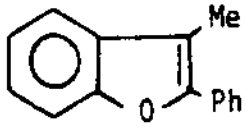
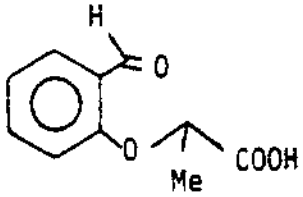
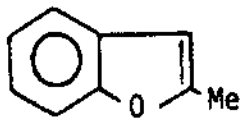
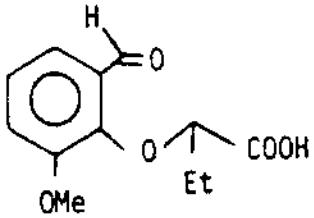
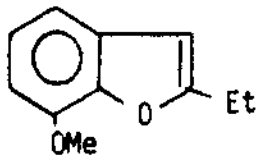
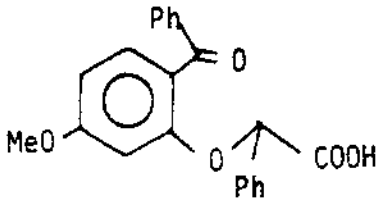
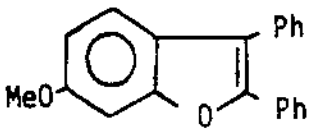
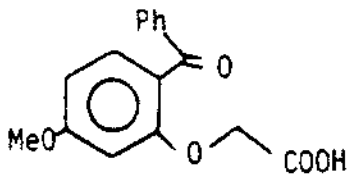
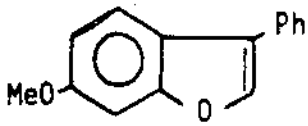
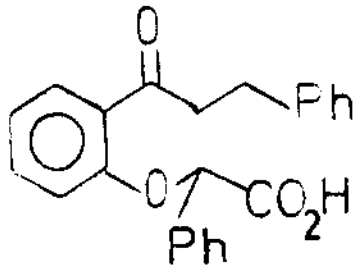
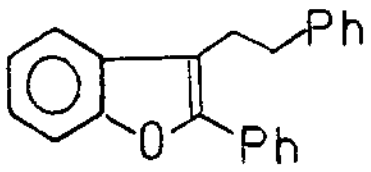
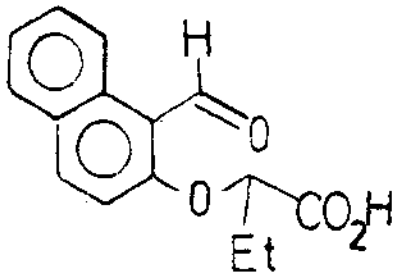
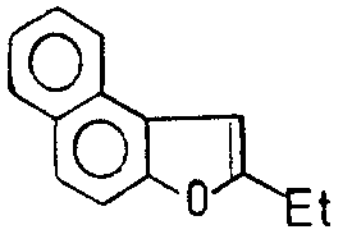
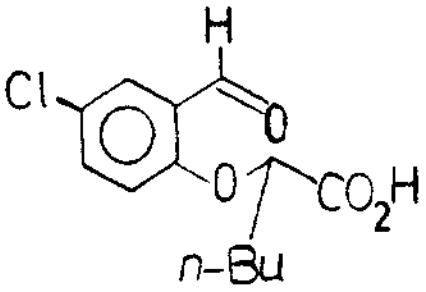
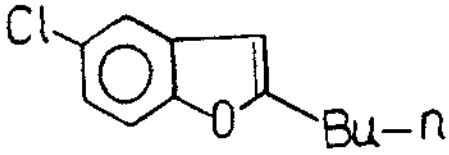
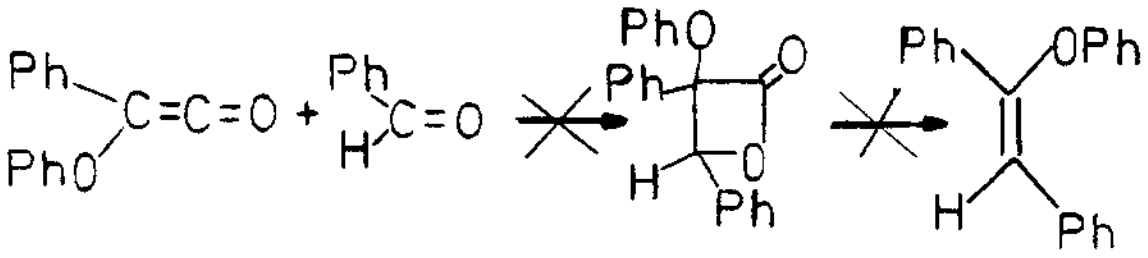
Entry	Acid, a	Benzofuran, b	Yield (%)
24			75
25			78
26			57
27			53
28			82
29			74

Table IV. Continued

Entry	Acid, a	Benzofuran, b	Yield (%)
30			89
31			74
32			72

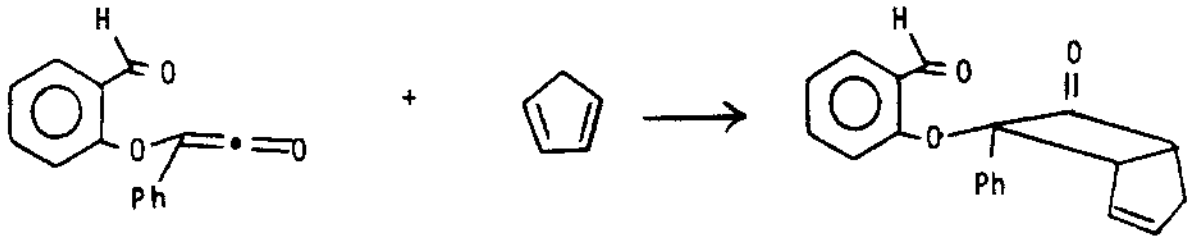
whether the carbonyl group is an aldehyde or ketene (37). To demonstrate the tremendous importance of the proximity effect of the two reacting functions, we attempted the intermolecular cycloaddition of benzaldehyde with phenoxyphenylketene under the same conditions as described above for the intramolecular cycloadditions (This is the exact counterpart of entry 24 in Table IV.). We found no evidence of the β-lac-



tone or the decarboxylated product, 1,2-diphenylphenoxyethene; however, a considerable amount of black tar was formed. This result is consistent with that reported by Staudinger (37).

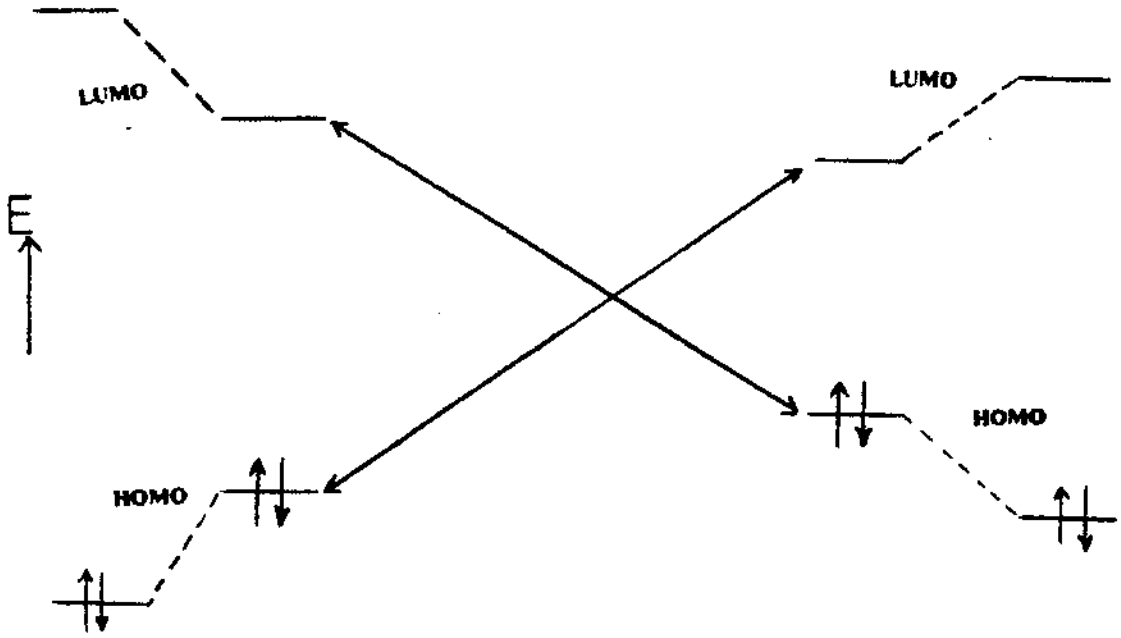
The described reaction is very similar to the well-known Perkin Reaction for the preparation of benzofuran (42); therefore, we felt it necessary to demonstrate that these reactions were indeed occurring via ketene intermediates. We were unable to detect the ketene and/or the β-lactone bands in the IR upon examining the spectra of the reaction solutions. However, we have demonstrated the intermediacy of phenoxyketenes in these reactions by trapping the ketene

with cyclopentadiene and isolating this cycloaddition product. The [2+2] cyclopentadiene adduct of the phenoxyketene (entry 24 in Table IV) has been isolated and characterized by the presence of the carbonyl band in the IR at 1783 cm^{-1} and by analysis of the ^{1}H- and ^{13}C-NMR spectra. Furthermore, the

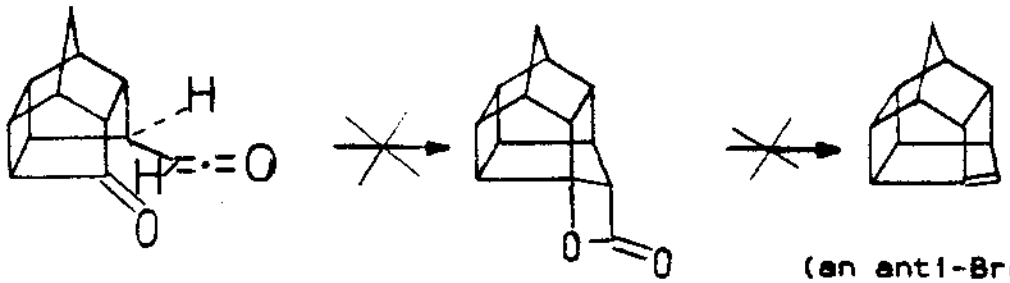


Perkin Reaction is normally only applicable to aromatic aldehydes and not ketones and of course the present procedure works quite well for ketone carbonyl groups as evidenced by entries 25, 28, 29 and 30 in Table IV.

The Frontier Orbital Theory and the aromaticity of the benzofurans also play important roles in this cycloaddition. In entry 24, for example, both of the ketene function and the carbonyl group are conjugated with a phenyl group. The effect of the conjugation is to raise both HOMO's but lower both LUMO's of the two reacting partners. Therefore, the two HOMO-LUMO interactions are both considerably enhanced as illustrated. Besides the intriguing benzofuran system, we have attempted the cycloadditions of a few other ketenes

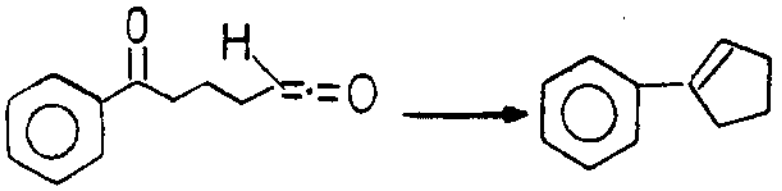


derived from their ketoacid precursors. However, the absence of the driving force which the benzofuran system posesses for the cycloaddition resulted in little or no cycloaddition. For instance, we have attempted the cycloaddition of 23c in Table III many times under a variety of reaction conditions but have not been able to detect or isolate the cycloadduct even though 23c provides the most favorable proximity. Also,

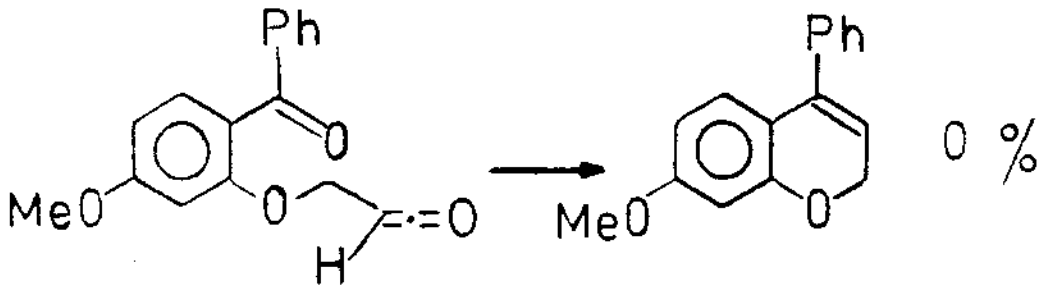


(an anti-Bredt compound)

the intramolecular ketene-carbonyl cycloadditions derived from 20c in Table III and 3-(2'-benzoyl-5'-methoxyphenoxy)-propanoic acid, where the carbonyl groups are conjugated with one or two phenyl groups, afforded only 7 % and 0 %, respectively, yields of the decarboxylated cycloadducts. The lack



7 %



0 %

of aromaticity of the products * and the unreactivity of the aldoketene are likely responsible for these results.

The benzofurans or coumarones have long been known to be widely used in many areas but principally in pharmacology. Most of the syntheses suffer from uncommon starting mate-

* In many cases where the ketene cycloaddition products suffer from high steric strain or are unstable for some reasons, the retro cycloaddition may occur appreciably and the cycloaddition reaction will be considered as being reversible. However, in the scheme on page 85, the decarboxylation of the initially formed β-lactone gives a very stable aromatic benzofuran thus driving the whole reaction sequence to the final product.

rials, complicated reaction conditions, poor yields or lengthy procedures (43, 44, 45, 46, 47, 48). The synthesis we describe is generally applicable to substituted benzofurans and should serve as a much improved procedure for the preparation of many substituted coumarones.

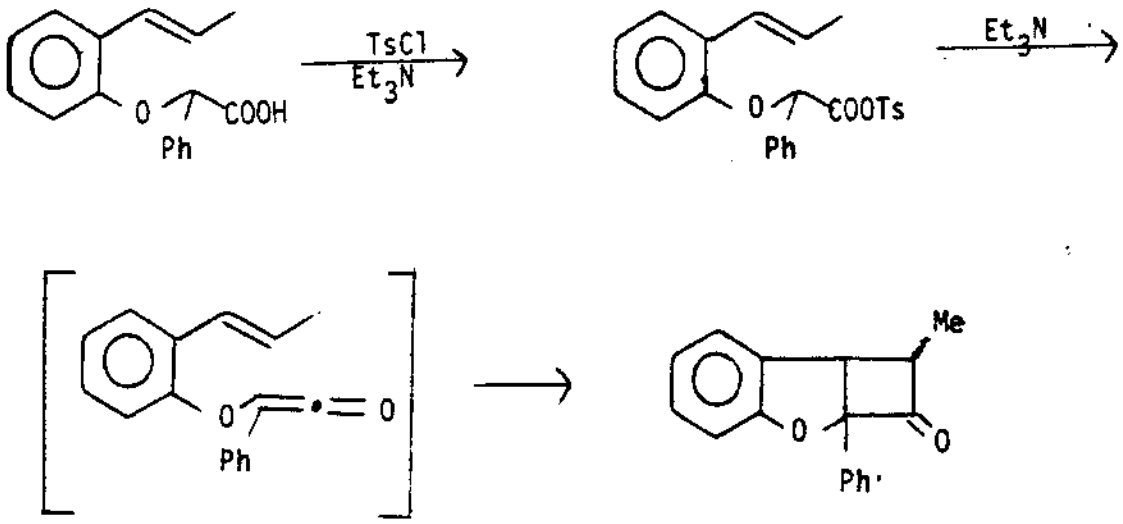
A New Preparation of Ketenes for Intramolecular Cycloadditions

During the course of this research on intramolecular cycloaddition reactions of ketenes, a new method for ketene generation was discovered as a collaboration effort with Wu (15). This method in most instances is a substantial improvement over existing methods.

The traditional methods for ketene generation include the dehydrohalogenation of an appropriately substituted acid halide and the zinc dehalogenation of an α-haloacid halide. Both methods normally require the preparation, isolation and purification of an acid halide.

This new preparative method utilizes tosylate as a leaving group rather than the traditional halide. It is not necessary to isolate the tosylate and hence, we have a one-pot synthesis from the carboxylic acid to the ketene cycloaddition product. This method is illustrated in the following scheme with (o-propenylphenoxy)phenylacetic acid (which is readily obtained from o-propenylphenol and α-bromophenylacetic acid). The acid is converted to the tosylate and subsequent triethylamine-promoted elimination of p-toluenesulfonic acid results in the formation of the corresponding phenoxyketene. Under our reaction conditions, the ketene spontaneously undergoes an intramolecular [2+2] cycloaddition to afford the corresponding tricyclic ketone. The overall

yield of the cycloadduct from the acid is 83 %. It is of

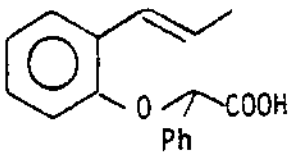
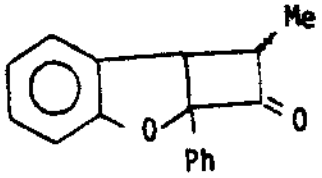
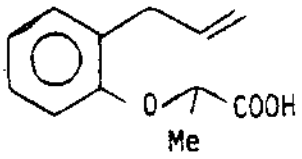
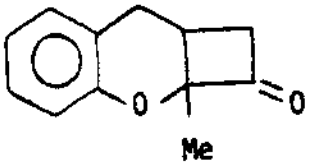
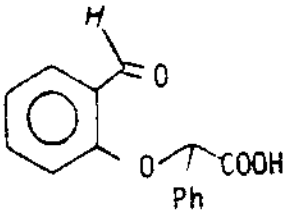
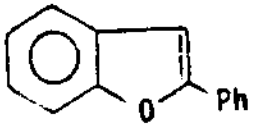
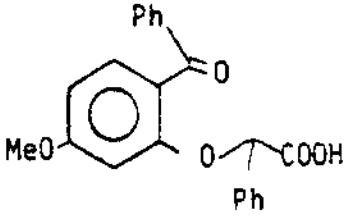
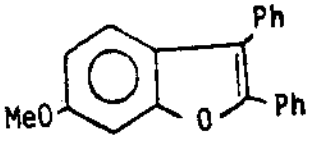
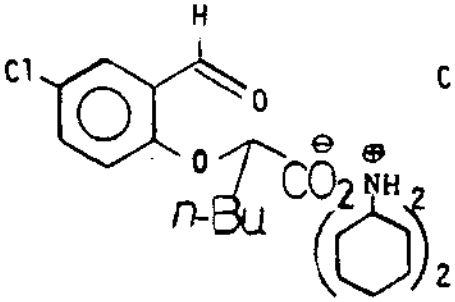
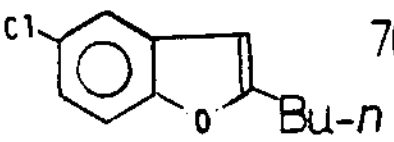


interest to note that the intermediate tosylate in this elimination reaction is in fact a mixed anhydride.

The results obtained by using this new procedure with four different intramolecular systems are contrasted with the conventional acid chloride procedure in Table V. It is apparent that the two procedures afford essentially equivalent yields of cycloadducts. The first two examples in Table V involve in situ cycloaddition of the phenoxyketene to a carbon-carbon double bond, and the latter two examples illustrate in situ cycloaddition of the phenoxyketene to the carbonyl group of an aldehyde and a ketone, respectively. The carbonyl group cycloadditions afford 2-oxetanones which spontaneously decarboxylate to the corresponding benzofurans.

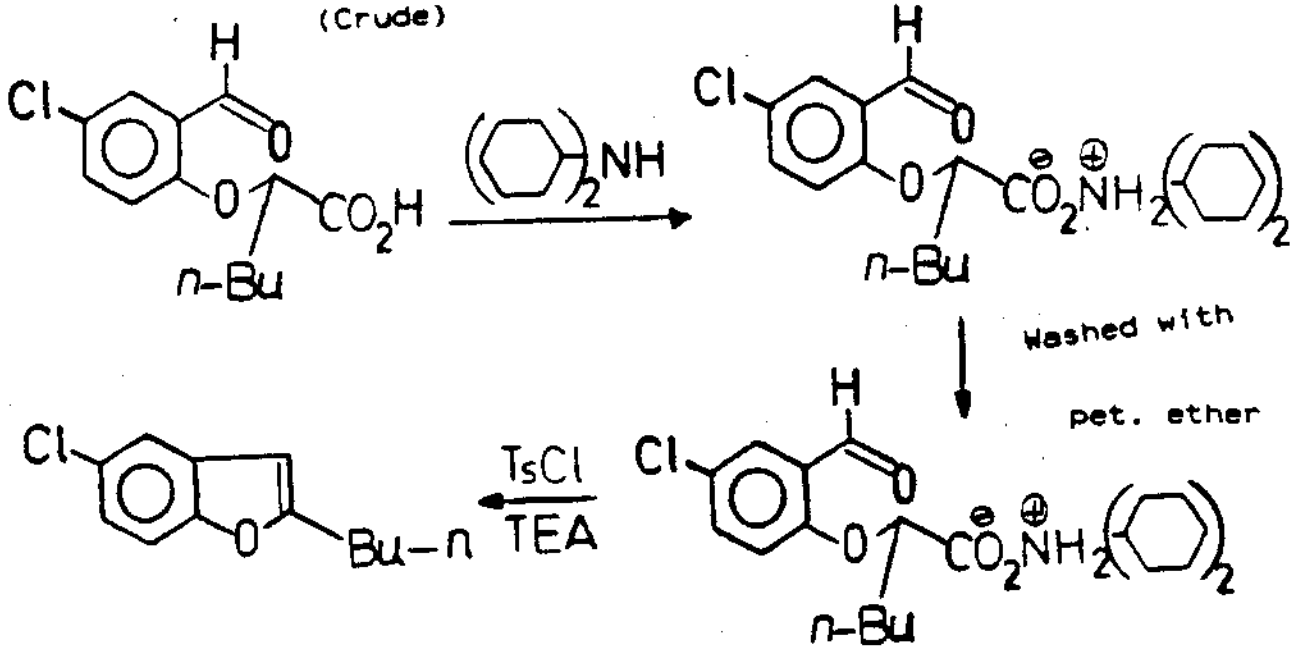
The one-pot preparation of the ketene cycloaddition

Table V. Intramolecular [2+2] Cycloadditions of Phenoxyketenes Generated by the Tosylate (OTs) and the Acid Chloride (X) Procedures

Entry	Acid or Ammonium Salt, a	Cycloadduct, b	Yield (%) (OTs)	Yield (%) (X)
5			83	85
8			50	43
24			78	75
28			84	82
33			70	—

product from the carboxylic acid via the ketene eliminates the acid halide preparation, isolation and purification step, thereby significantly simplifying the synthesis. The reagents used to prepare the acid chlorides (e.g., thionyl chloride and oxalyl chloride) are lachrymators and usually generate hydrogen chloride as a by-product. The inexpensive p-toluenesulfonyl chloride is much easier to handle than these lachrymators and the troublesome hydrogen chloride gas is not generated when an excess of triethylamine is used. We have tried other sulfonyl chlorides and found that benzenesulfonyl chloride and tosyl chloride are equally effective, however, methanesulfonyl chloride is not effective because this reagent reacts with triethylamine.

This tosylate procedure can also be used in such a manner that the purification of the precursor acids can be accomplished by preparing the dicyclohexylammonium salts and the washed ammonium salts can be reacted directly with tosyl



chloride as illustrated with entry 33. Advantage was taken of the outstanding crystallizing property of the dicyclohexylammonium salts (49). Usually, a dirty and oily crude carboxylic acid was dissolved in ethanol and upon treatment with about 1 equivalent of dicyclohexylamine the salt crystallized immediately. After adding an appropriate amount of petroleum ether, the salt was filtered, washed with petroleum ether and reacted by the one-pot tosylate procedure described above.

The utilization of the tosylate procedure for the preparation of diphenylketene (an isolable ketoketene, 37) from diphenylacetic acid is not effective because the initially formed diphenylketene competes for the diphenylacetic acid. We have demonstrated that diphenylketene is formed by this procedure as evidenced by the ketene band in the infrared spectrum of the reaction solution at 2100 cm^{-1}.

A serious drawback of the use of p-tosyl chloride is that the removal of this excess reagent requires a prolonged stirring with alkaline aqueous and clearly this would destroy such cycloadducts as β-lactones and β-lactams. It is proposed that trifuoromethanesulfonyl chloride can be used instead for this purpose due to its ease to remove under vacuum.

Many intermolecular cycloadducts have been reported to be potential biologically active compounds or important intermediates in organic synthesis. It is clear that Intra-

molecular ketene cycloaddition reactions as well as the secondary synthetic application of the intramolecular cycloadducts will prove to be a powerful synthetic tool for the organic chemist. This tosylate method provides an improved and simplified one-pot synthesis of the cycloadduct from the carboxylic acid. It is hoped that these initial results will help bring about more success in further related studies.

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