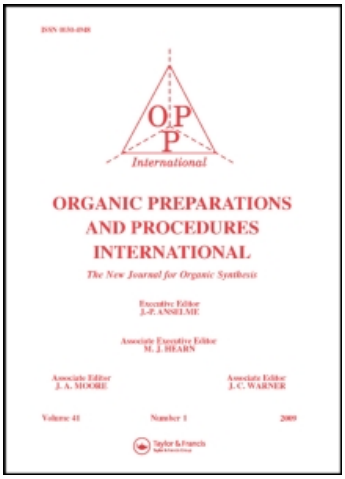

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RECENT PROGRESS IN TEE CONTROL OF CARBON VERSUS OXYGEN ACYLATION OF ENOLATE ANIONS

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RECENT PROGRESS IN THE CONTROL OF CARBON VERSUS OXYGEN ACYLATION OF ENOLATE ANIONS

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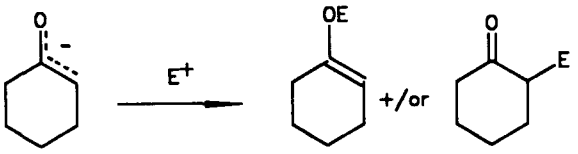
INTRODUCTION

Acylation of various atoms is one of the most generally useful and widely employed reactions available to the synthetic chemist. The variety of substrates and acylating agents reported in the literature is most impressive, and new reports continue to appear at a steady rate.

One of the oldest and most commonly exploited acylation reactions involves the reaction of an acylating agent with an enolate anion.[1] The Claisen condensation, in which esters self-condense in the presence of catalytic base, is an early example of such a process;[2] yields are generally very high since side reactions are minimal.

Despite their ubiquitous presence in organic synthesis, enolate acylation reactions often are complicated by the production of product mixtures. This phenomenon, which can be extremely problematical, arises from competition between the carbon and oxygen atoms of the enolate anion for the

electrophilic acylating agent:



Many factors are involved in an analysis of carbon versus oxygen acylation, and for any given variable, valid correlations exist for predicting its effect on the relative proportion of acylated products.[3] However, the myriad of parameters which mutually interact during an acylation reaction often make the reliable prediction of a specific reaction outcome very difficult indeed. With certain substrates, O-acylation competes or even predominates despite the utilization of conditions conducive to reaction at carbon. In fact, perhaps the only truly valid generalization concerning the control of carbon versus oxygen acylation is that the reaction is highly substrate-dependent, and that often the most that can be hoped for from the variation of controllable reaction parameters for a given molecule is an enrichment of the reaction mixture in the desired isomer.

It is the intention of this review to highlight current knowledge in the control of oxygen versus carbon acylation. Acylation reactions, especially those involving carbon acylation, have been the subject of several excellent reviews;[4] these should be consulted for detailed coverage of early work.

Although a brief summary of the effect of certain reaction variables on product ratios will be presented, the body of the article is organized by substrate type. Not only does this

represent the best correlation with respect to predictive utility, but should allow the most expeditious retrieval of primary literature precedent. Since carbon acylation is nearly always the desired outcome of an acylation reaction, several indirect methods for accomplishing this will also be highlighted.

I. GENERAL PRINCIPLES OF REGIOCHEMICAL CONTROL

A. Electrophile (acylating agent)

Carboxylic acid derivatives are typically employed as acylating agents; the most widely used are acid halides, anhydrides, and esters.[5] However, carbon dioxide, ketene, and other carbonyl-containing molecules are effective in some instances.[6] In general, the more reactive the electrophile, the greater the tendency toward oxygen acylation. This can be rationalized as a consequence of the greater electron density on the oxygen atom, causing kinetic acylation to occur at that site; the phenomenon is also predictable based on the known preference of more reactive alkylating agents for the harder oxygen atom.[7] Thus, acid anhydrides and chlorides are highly oxygen-selective, the former especially so. Mander's recent introduction of cyanoformates as highly carbon-selective acylating agents[8] also supports this generalization.

B. Enolate Countercation[9]

The nature of the metal cation associated with the enolate can profoundly affect acylation regioselectivity. Conditions conducive to ion pair separation facilitate oxygen acylation;

thus, alkali metal cations (Li^+, Na^+, K^+) and some divalent atoms (e.g., Zn^{++}) correlate with enhanced reaction at oxygen. This effect is compounded if comparatively polar solvents (dimethylformamide (DMF), dimethoxyethane (DME)) are employed. Conversely, the use of magnesium (either Mg^{++} or $MgBr^+$) or mercury tends to favor carbon acylation, due to strong association of the ion pairs and/or significant covalency in the metal-enolate bond. Not surprisingly, utilization of nonpolar solvents (diethyl ether) accentuates this effect.

C. Solvent[10]

As indicated above, the primary role of the solvent in these reactions is to influence the degree of association of the enolate anion/metal cation pair. Polar media, especially dipolar aprotic solvents such as dimethylformamide and dimethylsulfoxide, which solvate cations far more efficiently than anions,[11] tend to deshield the enolate oxygen from its cationic partner. This allows the greater electron density on the oxygen atom to attract the electrophile more effectively, and kinetic acylation at oxygen occurs preferentially.

D. Reaction Temperature

Since oxygen acylation is recognized as the kinetically preferred pathway, low temperatures usually increase the proportion of oxygen-acylated product.[3] This effect is not profound, though, and other reaction variables are considerably more important in dictating reaction outcomes.

E. Reagent Stoichiometry/Mode of Addition

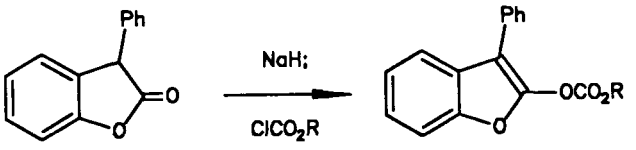
In the presence of excess acylating agent, O-acylation often predominates. If excess enolate is employed, however, C-acylation can become the main reaction.[12] Although the oxygen-acylated product (e.g., an enol ester or carbonate) is still rapidly formed in the latter case, it is capable of further reaction with the enolate in which it plays the role of acylating agent. A 3:1 enolate:electrophile ratio is typical,[13] and the excess of enolate also assures that the ß-diketone product will not be further acylated. Very low temperatures are common for reasons discussed above.

F. Nature of the Substrate

As mentioned previously, the most important variable affecting carbon/oxygen acylation ratios is the structure of the substrate itself. Both steric and electronic effects are operative, and can predispose a molecule toward one reaction pathway or another with sufficient magnitude that manipulation of the above parameters serves only to alter the product ratio somewhat. Obviously, steric interference surrounding the enolate oxygen or carbon atom toward the acylating agent will suppress the formation of the corresponding isomer. However, it appears that the extent of delocalization of the enolate charge also impacts heavily on product distributions. Generally, the more delocalized the enolate, the greater the proclivity for oxygen acylation, and the less effective the above variables are in overriding the phenomenon. In these cases, it is necessary to employ indirect methods for carbon acylation; several very elegant examples are provided in Section V.

II. PREDOMINANT OXYGEN ACYLATION

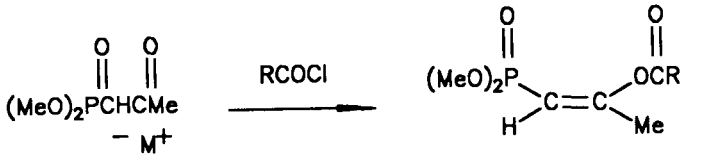
Highly delocalized enolates are, of course, prime targets for O-acylation even if this is not desired; this was demonstrated for 3-phenylbenzofuranone 1 which afforded enol carbonates 2 despite all efforts to achieve carbon



1 R=alkyl 2

acylation.[14] For other substrates, achieving predominant enolate acylation at oxygen generally requires conditions which assure a rapid reaction and which favor breakup of the enolate/cation contact pair. It appears that the former criterion is more important, since, if highly reactive acylating agents are employed, even solvents like tetrahydrofuran (THF) allow nearly exclusive O-acylation.[15]

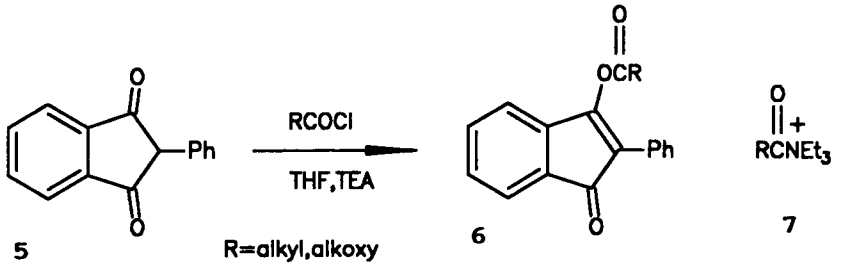
A series of phosphonate anions 3 was shown to afford exclusive oxygen acylation with acid chlorides, regardless of the countercation employed.[16] Simultaneous coordination of the phosphoryl and acid chloride oxygen atoms by the metal cation resulted in the production of exclusively Z phosphoryl



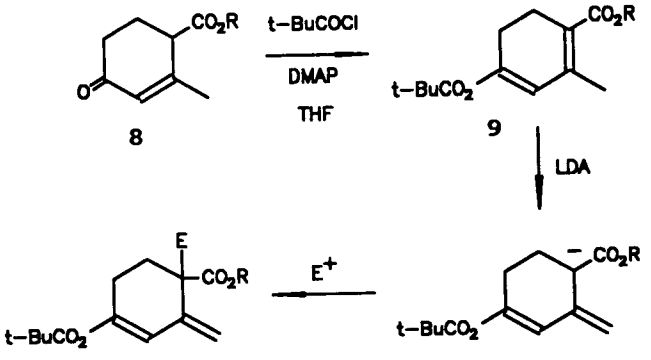
3 M=Li,Na,K R=MeO,aryl 4

enol esters 4; this explanation is borne out by the E/Z mixtures which resulted from treatment of the same enolates with alkyl chlorides.

A series of plant growth regulators 6 was prepared via acylation of 2-phenyl-1,3-indanedione 5 with either acid chlorides or chloroformates in THF in the presence of



triethylamine (TEA).[17] Although not explicitly addressed in the report, the function of the amine was probably to form the highly reactive acylated ammonium salt 7. Hagemann's ester 8, R = Et) and its t-butyl analog (8, R = t-Bu) were successfully O-acylated in THF, this time using 2.5 equivalents of either dimethylamino-pyridine (DMAP) or tetramethylethylenediamine



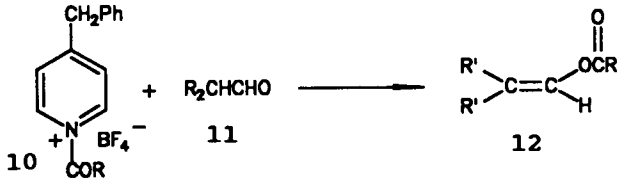
R	E^+	E	Yield*
Et	MeI	Me	80%
Et	$H_2C{=}CHCHO$	$H_2C{=}CH(OH)$	68%
t-Bu	$ClCO_2Me$	MeO_2C	56%
Et	$H_2C{=}CHCO_2Me$	$MeO_2C(CH_2)_2$	70%
Et	TsCl	Cl	100% (crude)

*purified unless otherwise noted

(TMEDA).[18] It is likely that these amines served both to

catalyze formation of the enolate and to form reactive acylating agents. As indicated, the resulting dienol esters 9 can be easily deprotonated with lithium diisopropylamide (LDA) at C-1 and treated with a variety of electrophiles.

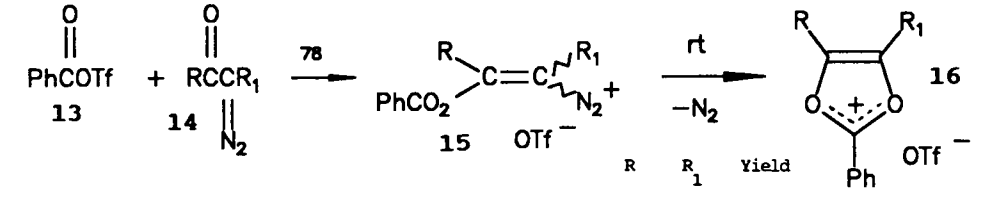
A most dramatic example of the utilization of highly reactive acylating agents involved the preparation and isolation of acylpyridinium tetrafluoroborate salts 10, which reacted with enolizable aldehydes 11 in ether to afford exclusively enol esters 12.[19] Although the yields were



R	R'	Yield
Ph	Ph	39%
Ph	Me	41%
i-Pr	Ph	75%
i-Pr	Me	18%
PhCH=CH	Ph	61%
p-MeOC6H4	Ph	69%

variable (18-69%), the efficacy of the reaction for simple aldehydes such as isobutyraldehyde is impressive since oxygen acylation of such substrates is so difficult using other approaches.

Acyl triflates are known as superior acylating agents, and recently figured predominantly in a preparation of vinyl diazonium (15) and 1,3-dioxolium (16) salts.[20] Thus, benzoyl triflate (13) reacted at -70° with a-diazo ketones 14 to form



R	R_1	Yield
Ph	Ph	74%
Me	Me	75%
Ph	H	66%

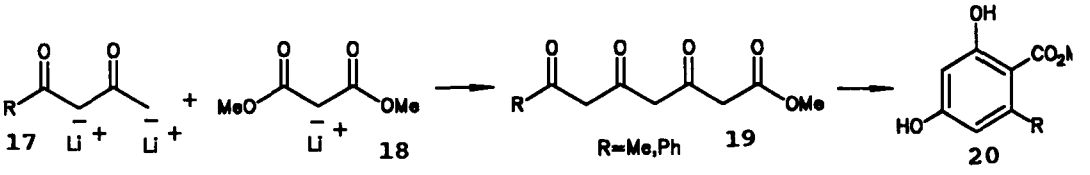
the intermediate alkenediazonium salts 15, which, upon warming to room temperature, produced dioxolium salts 16 via loss of nitrogen and cyclization of the derived vinyl cation.

III. PREDOMINANT CARBON ACYLATION

From a synthetic viewpoint, carbon functionalization is usually the more useful of the two possible outcomes of enolate acylation. Accordingly, the vast majority of reported selective reactions involve techniques for C-acylation. As mentioned previously, however, selectivities are quite substrate-dependent; this is particularly evident for this series of reactions.

A. ß-Diketones and Related Molecules

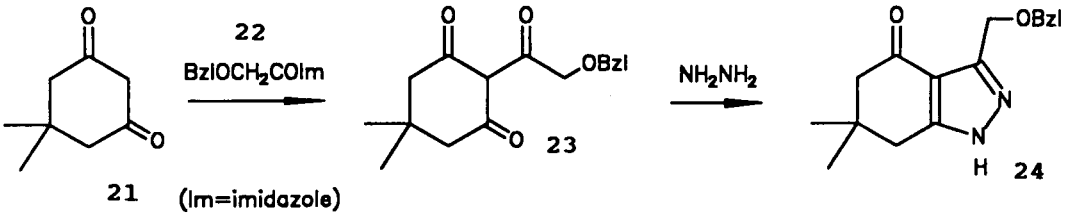
A general synthesis of 3,5,7-triketo esters 19 involved the acylation of 2,4-pentanedione and related compounds as the dilithio derivatives 17; the acylating agent was the lithium salt of dimethyl malonate (18).[21] Carbon acylation occurred on



the chain terminus and virtually no bis-acylation could be detected. Exposure to mild acid effected cyclization to methyl orsellinate (20, R = H) and derivatives.

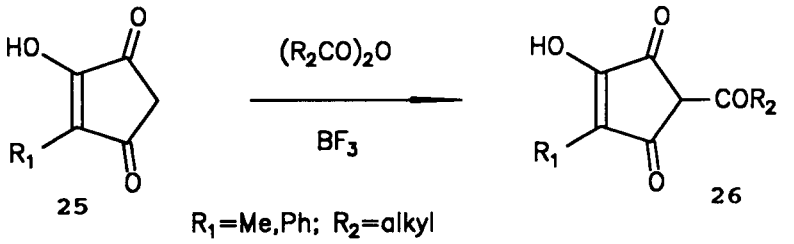
Dimedone (21) was C-acylated in moderate yield with benzyloxyacetic acid in the presence of 1,1'-carbonyldi-imidazole (CDI); the active acylating agent is obviously the

acyl imidazole 22.[22] Reaction of the trione 23 with



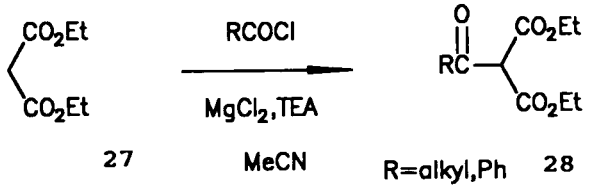
hydrazine completed the synthesis of indazolones 24.

Extensively enolized substrates such as derivatives of cyclopentane-1,2,4-trione (25) are difficult candidates for carbon acylation. Acylated triones 26 were prepared in low yield (14-38%) by treatment with alkyl anhydrides in the



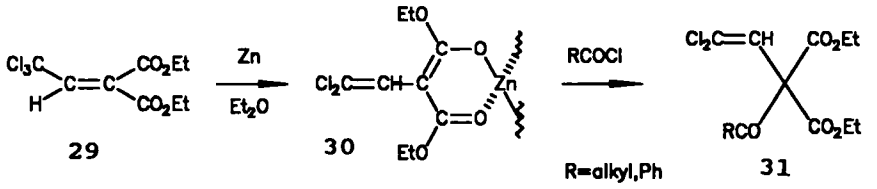
presence of excess BF_3 (introduced as the gas).[23] Either 1,2-dichloroethane or the acylating agent were employed as the solvent. Presumably, the function of the BF_3 is to coordinate to the oxygen atoms and thus direct the electrophile to carbon.

Diethyl malonate (27) can be carbon-acylated in high yield



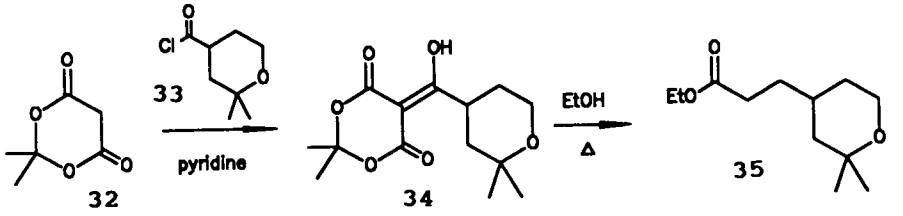
by acid chlorides in the presence of TEA and a stoichiometric quantity of magnesium chloride to afford keto diesters 28.[24] The reaction, carried out in acetonitrile, is possible with both alkyl and aryl acid chlorides. It is likely that the magnesium functions in the same manner as did BF_3 above - to direct carbon acylation through coordination to oxygen.

A somewhat less direct method for the carbon acylation of malonates involves the reaction of zinc metal with ethyl 2,2,2-trichloroethylidenemalonate (29) to afford the coordinated zinc enolate 30.[25] Electrophilic attack by acid



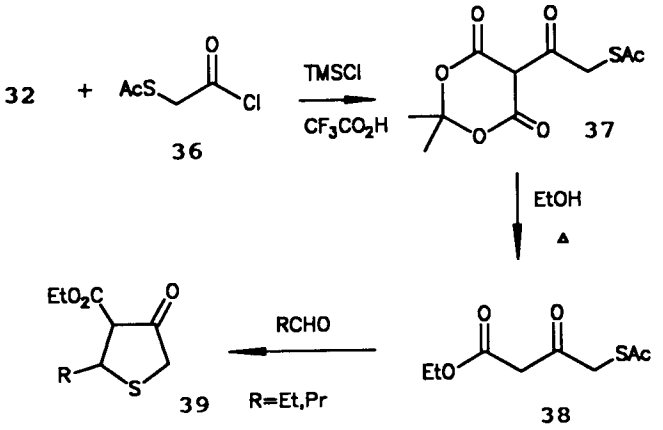
chlorides results in the formation of the previously-undescribed ethyl acyl (2,2-dichlorovinyl)malonates 31.

Meldrum's acid (32) has functioned as a useful alternative to malonic esters for many years. Carbon acylation of this cyclic diester is more facile than for cyclic diketones, since ester enolates typically are C-acylated preferentially. Thus, acid chloride 33 reacted with Meldrum's acid in the presence



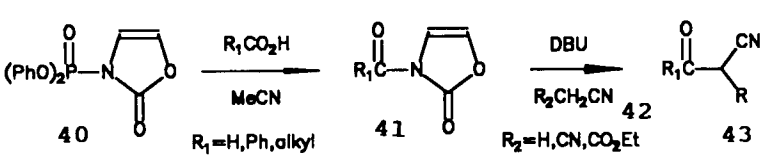
of pyridine to afford the keto derivative 34, which was converted to the tetrahydropyranyl ß-oxopropionate 35 by treatment with ethanol at reflux.[26]

An interesting thiophene synthesis involved the carbon acylation of Meldrum's acid with acetylthioacetyl chloride (36) in dichloromethane in the presence of chlorotrimethylsilane and trifluoroacetic acid.[27] The acetylated product 37



was cleaved with refluxing ethanol as noted above to afford keto ester 38, which, when allowed to condense with alkyl aldehydes, was transformed in 25% yield to the tetrahydrothiophenones 39.

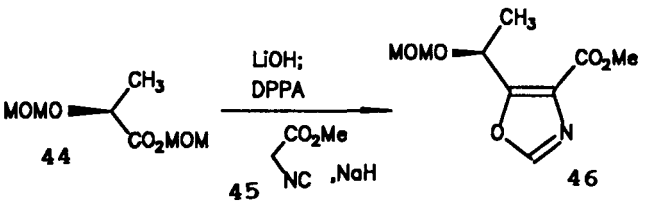
Malononitrile (42, R = CN) and ethyl cyanoacetate (42, R = EtO_2C) have been carbon-acylated in high yield with the acylating agent 41 formed by the interaction of carboxylic



R_1	R_2	Yield
Ph	H	59%
Ph	CN	87%
Ph	CO_2Et	96%

acids with diphenyl-2-oxo-3-oxazolinylphosphonate (40).[28] With acetonitrile serving as solvent in these cases, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) being employed to catalyze enolate formation, the acylated products 43 were formed in approximately 90% overall yield.

Direct carbon acylation of methyl isocyanoacetate (45) is similarly possible with a wide selection of carboxylic acids, utilizing diphenyl phosphorazidate ($(PhO)_2P(O)N_3$, DPPA) as the activating reagent. The methoxymethyl (MOM) ester 44, as the lithium salt, was treated with DPPA in DMF, followed by the addition of the sodium salt of 45 (formed via sodium hydride), to provide the oxazole 46 in 70% yield.[29] This general



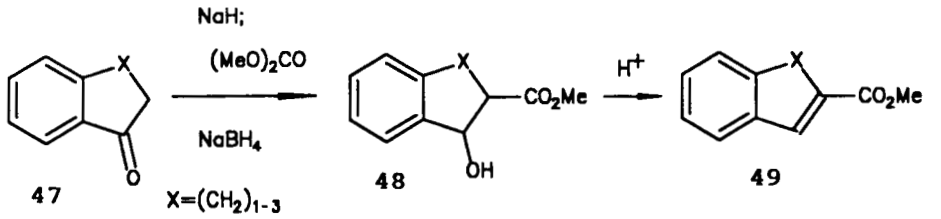
protocol has enabled synthetic access to a variety of medicinally important compounds, such as L-daunosamine,[29] mugineic acid,[30] and prumycin.[31]

B. Ketones

Simple ketones are typically carbon acylated employing alkyl carbonates in nonpolar solvents such as benzene or diethyl ether. Nevertheless, oxygen acylation is the primary competing reaction, and purification can be difficult if the physical constants of the C- and O-acylated products are similar. An early report demonstrated the predominant carbon

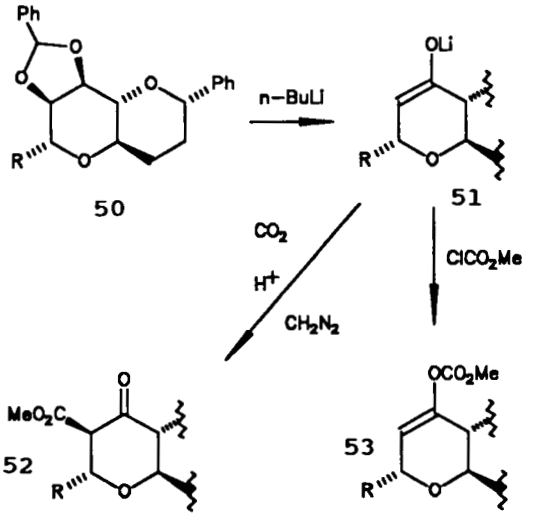
acylation of simple ketone (sodium) enolates, which were formed in liquid ammonia and then treated with acid chlorides subsequent to exchanging the solvent for ether.[32]

Both 1- and 2-tetralone were deprotonated with sodium hydride in benzene and then C-acylated with diethyl carbonate to afford the corresponding ß-keto esters in 89% and 73% yield, respectively.[33] Similar cyclic ketones 47 were treated



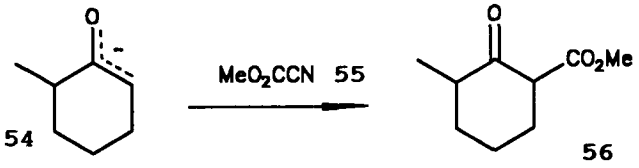
analogously, whereupon the resulting ß-keto esters were reduced with sodium borohydride to give hydroxy esters 48, which were dehydrated to afford a series of benzo cycloalkenes 49.[34]

The effects of different acylating agents was clearly



demonstrated in an acylation study of carbohydrate enolates.[35] C-Glycoside 50 was treated with n-butyllithium, removing the protecting group and generating the enolate 51, whereupon quenching with methyl chloroformate produced enol carbonate 53 as the primary product. Conversely, acylation with carbon dioxide, followed by protonation and esterification, afforded ß-keto ester 52 through carbon acylation.

Recently, a new reagent, methyl cyanoformate (55), was introduced which is completely regioselective for carbon acylation.[8] Ketone enolates (e.g., 54), formed with LDA in

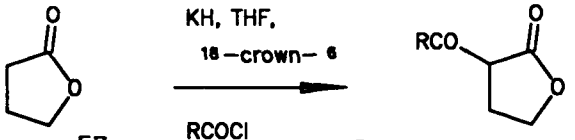


54 56

THF/hexamethylphosphoramide (HMPA), are treated at -78° with methyl cyanoformate for ten minutes. Standard aqueous workup affords the corresponding ß-keto esters 56 in high yield. This protocol appears to be quite general, and the method has already found use in several recent syntheses.[36]

C. Esters, Lactones, and Related Molecules

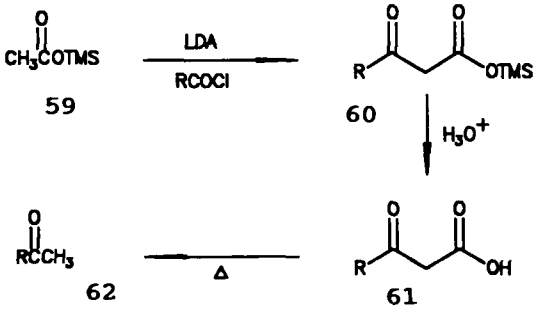
Ester enolates typically react with acid chlorides at



57 R=Me,Ph 58

carbon; oxygen acylation is usually not problematical. Butyrolactone (57) and several alkylated derivatives were treated with a solution of potassium/18-crown-6 in THF and the resulting enolates were treated with acid chlorides to afford acylated butyrolactones 58 in very high yield.[37]

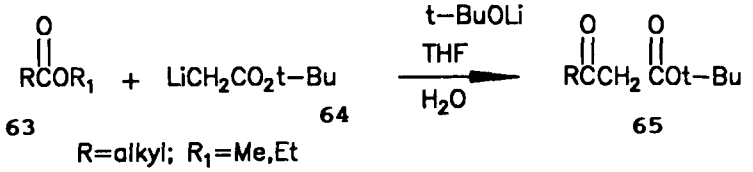
A useful sequence to ß-keto acids and methyl ketones involves the deprotonation of trimethylsilyl acetate (59, R = H) with LDA, followed by acylation with acid chlorides.[38]



R	Yield (GLC)
Ph	98%
p-MeC6H4	80%
Me3C	94%
Me2CH	99%
n-C3H7	77%

The derived silyloxy esters 60 were hydrolyzed to ß-keto acids 61, which could be decarboxylated to methyl ketones 62.

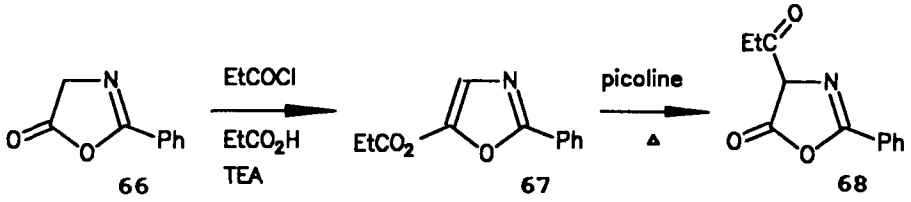
A novel crossed Claisen condensation was recently reported in which t-butyl lithioacetate (64) is treated with esters (63) or butyrolactone. Excess lithium t-butoxide is present



in some cases to deprotonate the product, which, unless

enolized, might react with additional nucleophile.[39]

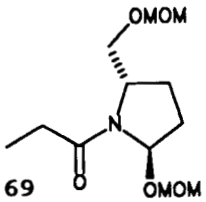
Oxazolinones such as 66 undergo carbon acylation when treated with acid chlorides in the presence of TEA (other catalysts are also effective), followed by exposure to picoline.[40] The interesting two-step mechanism involves initial formation of oxazoline 67, which rearranges in picoline



to the acylated product 68. A similar sequence occurs during the well-known Dakin-West reaction, which will be addressed in greater detail in a later section.

D. Amides

The acylation of amide enolates is exploited primarily in the realm of chiral synthesis, wherein the amine used to form the amide is optically enriched.[41] Oxygen acylation, in competition with reaction at carbon, is virtually never encountered; thus, LDA in THF at -78° followed by treatment with an acid chloride constitute typical acylation conditions. A number of chiral auxiliaries have been successfully employed, including pyrrolidine derivatives such as 69[42] and oxazolinones 70 and 71.[43] The latter two compounds form a pair which affords highly diastereoselective acylation reactions in either desired sense. Additionally, the ß-keto



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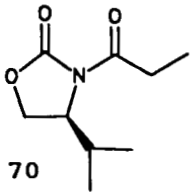

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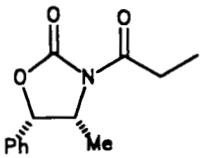

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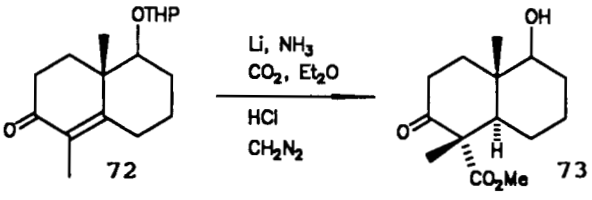
amides thus produced can be very selectively reduced to either the syn or anti ß-hydroxy amides.[44,45]

E. Enones

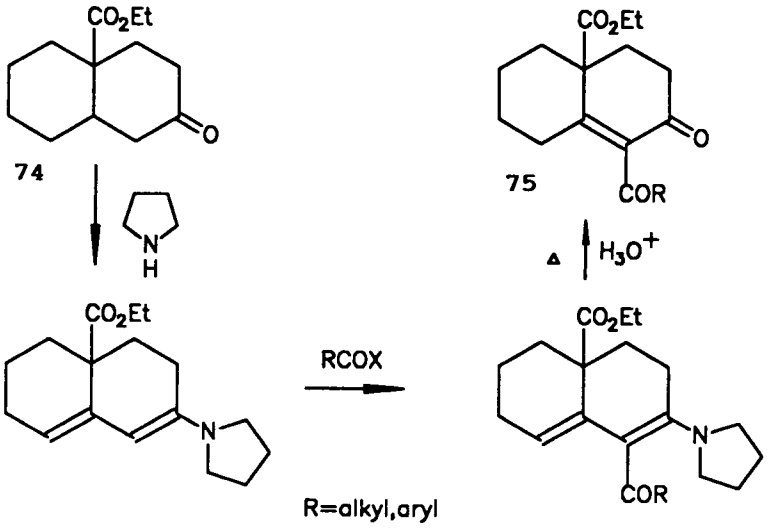
During a total synthesis of podocarpic acid, the direct acylation of enone 72 was attempted under a variety of conditions.[46] A modest yield of the carbomethoxy derivative 73 was finally obtained via enolate formation with lithium in



72 73

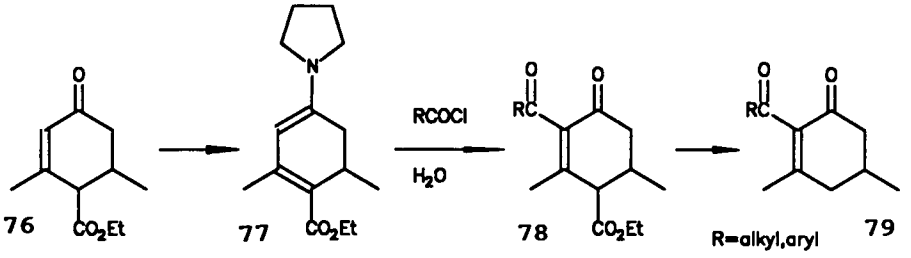
liquid ammonia, solvent exchange to ether and treatment with carbon dioxide gas, acidification, and esterification with ethereal diazomethane. Extensive chromatography was required to obtain pure material; thus, another synthetic approach was devised.

Alpha acylation of some conjugated enone systems is possible, however, using appropriate reaction conditions and with suitable substrates. A careful study meant to define the optimum protocol for this process, using bicyclic enone 74 as



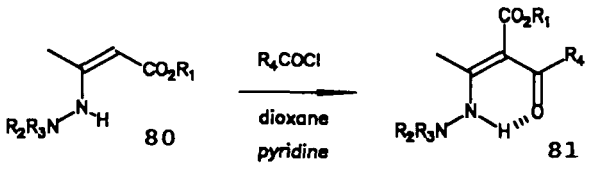
the test substrate, compared three methods of enolate (or equivalent) formation: sodium ethoxide in ethanol, sodium in liquid ammonia, and formation of the pyrrolidine enamine.[47,48] The enamine method was found to be superior due to increased yield and ease of workup, and the ß-keto enone 75 was formed in high yield following hydrolysis of the dienamine functionality. In no case was acylation at oxygen or another potential carbon detected.

The enamine protocol was also employed successfully for



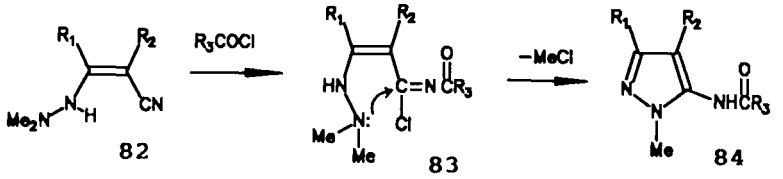
the preparation of a series of ß-keto enones 76 related to Hagemann's ester.[49] The dienamine 77, formed in the usual manner via azeotropic removal of water, was treated with acid chlorides and subsequently hydrolyzed to afford the ß-keto enones 78, which following saponification/decarboxylation finally afforded the acylated cyclohexenone derivatives 79.

An intriguing synthesis of 5-(acylamino)pyrazoles 84 examined related chemistry for the carbon acylation of hydrazino crotonate esters 80.[50] These substrates were treated with acid chlorides in dioxane in the presence of one equivalent of pyridine to afford the acylated derivatives 81 in moderate yield. The sequence was repeated with analogous



R_1	R_2	R_3	R_4	Yield
Me	Me	Me	Ph	66%
Et	Me	Me	p-ClC$_6$H$_4$	63%
Et	-(CH$_2$)$_2$O(CH$_2$)$_2$-		Me	60%
Et	-(CH$_2$)$_2$O(CH$_2$)$_2$-		Bzl	55%

acrylonitriles 82, but in these cases acylation at nitrogen occurred to yield the acyl chloro imines 83; these spontaneously expelled chloromethane in a ring closure process to afford the pyrazoles 84 in quite high yield.



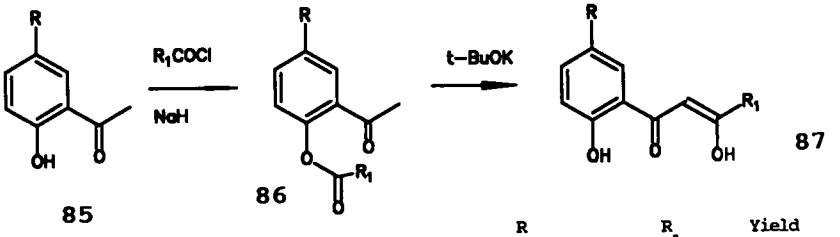
R_1	R_2	R_3	Yield
MeS	CO$_2$Me	Ph	62%
H	CN	CH$_2$Cl	76%

IV. INDIRECT METHODS FOR CARBON ACYLATION

Despite the considerable success achieved in exerting regiochemical control of carbon versus oxygen acylation of enolate anions, the considerable dependence of the reaction course upon substrate structure has spawned a wide variety of synthetic alternatives to direct carbon acylation. These methods fall into three basic categories. Oxygen-to-carbon acyl transfer reactions effect a migration of the acyl functionality from the enol ester (or carbonate) which forms kinetically to an adjacent carbon atom. A variety of umpolung-type carbonyl cation synthons are known, which are specific for attachment at carbon and transformable to the desired acyl derivative following the attachment. Lastly, several "enolate equivalents" react with typical acylating agents; an example already noted is enamine derivatives of enones.

A. Oxygen-to-Carbon Acyl Transfer Reactions

The Baker-Venkataraman reaction, which has been

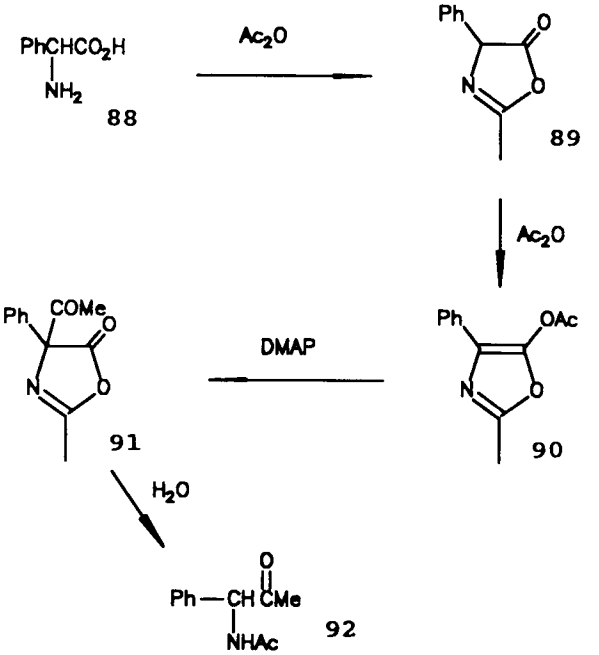


85 86 87

R	R_1	Yield
H	$CH_3CH{=}CH$	54%
H	C_5H_{11}	52%
$H_2C{=}CHCH_2O$	$CH_3CH{=}CH$	55%
$H_2C{=}CHCH_2O$	$CH_3(CH{=}CH)_2$	63%
H	Ph	64%

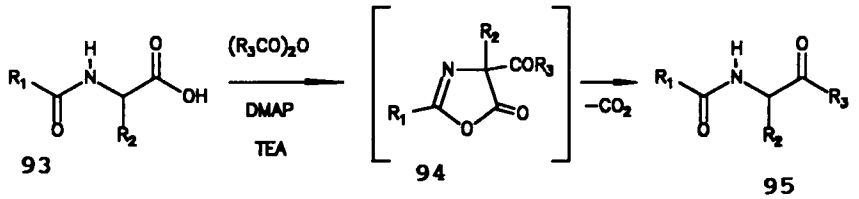
extensively exploited in flavone chemistry,[51] is one of the first examples of an oxygen-to-carbon acyl transfer reaction. Its primary function is the acylation of methyl ketones which are ortho to a phenolic hydroxyl group, as in 85. The extreme acidity of phenols makes direct carbon acylation impossible in such systems, and phenoxy esters 86 always result. However, treatment of these compounds with potassium t-butoxide/t-butanol effects a high-yield transfer reaction, accompanied by a deep red coloration characteristic of the process and affording ß-diketones 87. Traditionally applied to aromatic or heteroaromatic acyl groups, this ß-diketone synthesis has been extended to encompass aliphatic groups as well,[52] and was recently utilized to construct the key intermediate in a total synthesis of 11-deoxydaunomycinone.[53]

The conversion of amino acids (88) to acetamido ketones 92 with acetic anhydride is known as the Dakin-West



reaction.[54] Conventionally catalyzed by a variety of bases, it involves acetylation of the amine function, cyclization to the azlactone (oxazolinone) 89, oxygen acylation of the carbonyl group, acyl transfer to the adjacent carbon atom, and finally hydrolysis. The process has recently been revived due to the observation that "hypernucleophilic" acylation catalysts such as DMAP[55] allow the reaction to proceed rapidly and in very high yield.[56] The initially-formed enol ester 90 is treated with DMAP, which itself becomes acylated. The resulting ion pair reacts at carbon under equilibrating conditions to produce the carbon-acylated product 91.

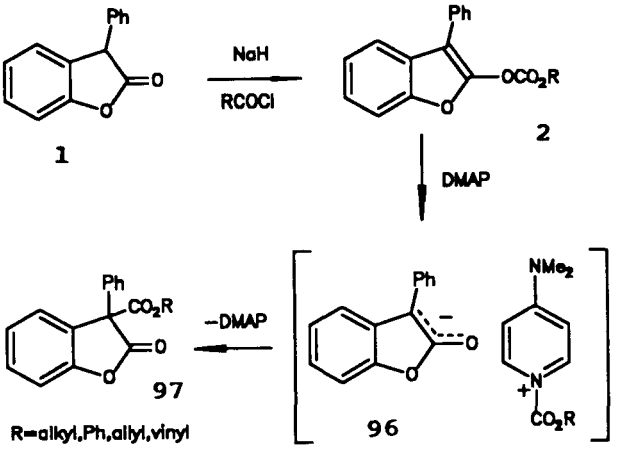
The Dakin-West procedure was recently extended to the preparation of ketomethylene peptide analogs 95.[57] N-acyl amino acids 93 were treated with acid anhydrides in the presence of DMAP and TEA to form the carbon-acylated oxazolones 94, which



underwent facile decarboxylation <u>in situ</u> to afford the desired molecules. This sequence is effective with di- and tripeptides as well as amino acids.

The resistance of 3-phenylbenzofuranone (1) toward carbon acylation mentioned earlier was addressed using DMAP technology.[15] The enol carbonates 2 were treated with a catalytic amount of DMAP in dichloromethane, resulting in a

quantitative rearrangement to the carbon acylated isomers 97.



Interestingly, the acyl transfer, which required only two minutes, was accompanied by an intense, deep blue coloration; this was ascribed to the formation of the ion pair 96 which functioned in these cases as an efficient donor-acceptor complex.

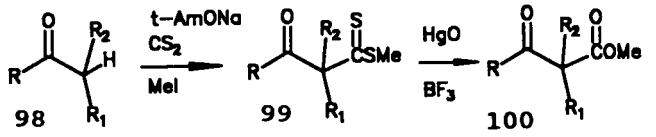
The ability of DMAP to function as a carbon acylation catalyst has been examined in other contexts. With simple ketone enolates, the inclusion of DMAP in the reaction mixture increases the proportion of oxygen acylation.[58] The acylation of more delocalized substrates, e.g., aryl acetic acid esters, seems to be relatively unaffected by the catalyst.[59] However, molecules such as diaryl acetic acid esters, which closely resemble the phenylbenzofuranones, are C-acylated in the presence of DMAP and O-acylated without it.[60] It appears that the ability of the enolate to function as a leaving group is highly correlated to the ability of DMAP to function as a carbon acylation catalyst. The increased incidence of oxygen acylation in simple ketones is consistent with the heightened

reactivity of the electrophile, as seen previously.

B. Carbonyl Cation and/or Anion Synthons

During the past several years, several ingenious methods have been developed for circumventing difficult carbon acylation problems, or for extending the generality of a given acylation method. Most of the protocols involve umpolung-type carbonyl anion synthons,[61] wherein a masked carbonyl capable of acting as a nucleophile is employed to form the carbon-carbon bond. As shall be seen, this is especially useful when ß-acylation of an enone system ("conjugate carbonyl addition") is desired.

Unsymmetrical ketones such as **98**, containing a tertiary center, are known to acylate at the less-substituted carbon atom, since the ß-keto ester resulting from attack at the tertiary center cannot be deprotonated and thus provide a needed driving force. Carbon disulfide reacts exclusively at



R	R_1	R_2	Yield
Ph	Me	Me	58%
Me	Me	Me	70%
-CH(Me)$(CH_2)_3$-		Me	45%

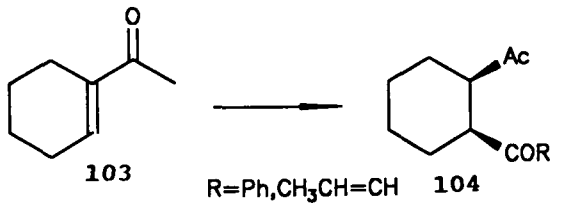
the tertiary center, however, and in the presence of iodomethane, the ß-keto dithioester **99** is formed in high yield, whereupon treatment with mercuric oxide/boron trifluoride affords the corresponding ß-keto ester **100**.[62] The sequence is successful with a variety of substrates.

Conjugated enone systems commonly add acyl anion synthons

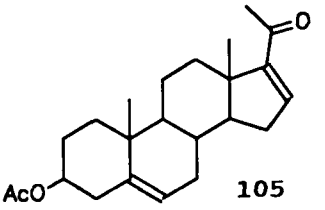
in a 1,4 fashion to afford 1,4-diones. Obviously, standard acylating agents are inappropriate for this application. Typical reagents include thio acetals such as 101[63] and cyanohydrin ethers[64] (e.g., 102). The latter were recently

101 102

utilized in the preparation of 16-acyl pregnane derivatives.[65] 1-Acetylcyclohexene (103) was employed as a model substrate, and indicated that the anions derived from 102 added stereoselectively cis to the acetyl group, after which base-catalyzed equilibration could be invoked to provide the trans isomers. Hydrolysis with aqueous potassium carbonate unmasked



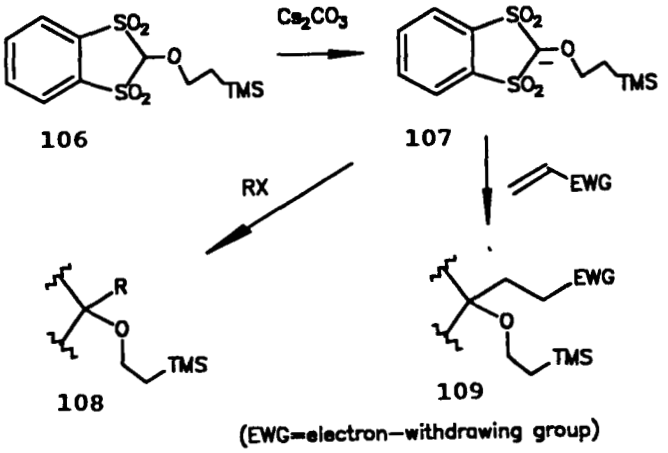
103 R=Ph,CH_3CH=CH 104



105

the carbonyl groups. Exposure of the steroid 105 to the same conditions afforded the trans isomers directly, probably due to the conformational rigidity of the fused ring system.

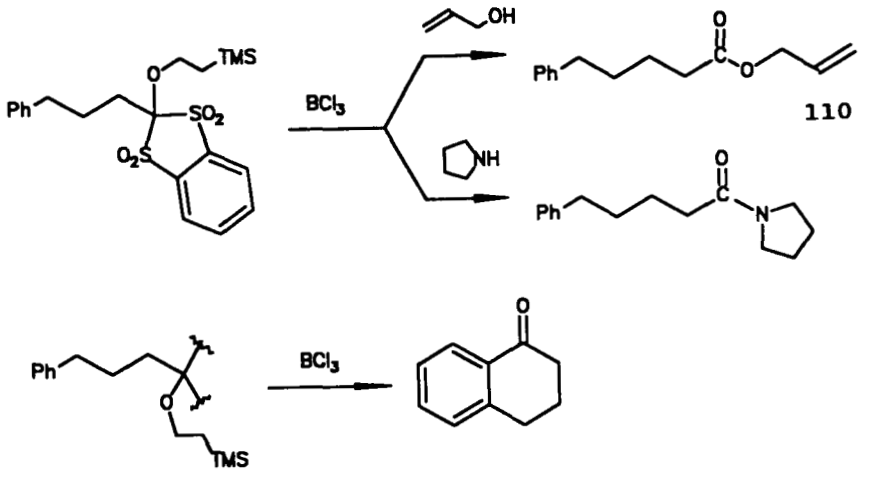
The alkoxy(bis)sulfonylmethane derivative 106 has been exploited as a unique carbonyl 1,1-dipole synthon, capable of first functioning as an acyl anion which can be alkylated, then as a cation capable of attack by nucleophiles.[66] 106 is deprotonated with cesium carbonate,



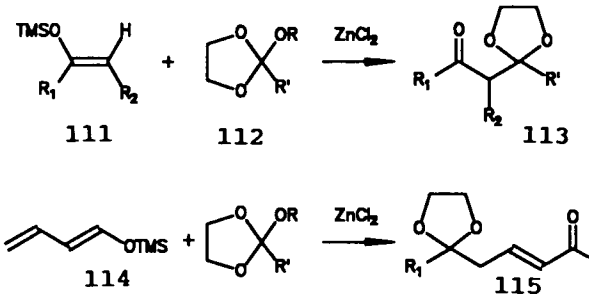
RX	EWG	Yield
$H_2C{=}CH(CH_2)_8Br$	—	73%
$Ph(CH_2)_2Br$	—	81%
$Ph(CH_2)_3I$	—	87%
—	$COCH_3$	64%
—	CN	46%
—	SO_2Ph	74%

whereupon reaction of the enolate 107 with alkyl halides or Michael acceptors (these cases are catalyzed by $Ni(acac)_2$) affords the adducts 108 or 109, respectively. Allylic alkylation is also possible under phase-transfer conditions.

At this point, ionization of the sulfone is effected with boron trichloride, whereupon subsequent reaction with nucleophiles such as alcohols, amines, or even aromatic rings (in an intramolecular ring-forming reaction) affords the corresponding carbonyl-containing derivatives (e.g., 110).

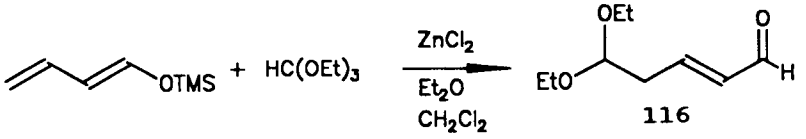


2-Alkoxy dioxolanes such as 112, when treated with Lewis acids (e.g., zinc chloride), function as carbonyl cation



R_1	R_2	R	R'	Yield
Me_3C	H	Et	Et	62%
$-(CH_2)_3-$		Et	Et	70%
Ph	H	Me	Ph	88%
$-(CH_2)_4-$		Me	Ph	70%

equivalents in the acylation of trimethylsilyl enol ethers 111.[67] This protocol is quite valuable in that monoprotected ß-diketones such as 113, ordinarily difficult to come by, are easily produced. The vinylogous analogs of 113 (e.g., 115) are accessible via reaction with dienol ethers 114, and the synthesis of acetals (rather than ketals) requires only the substitution of ortho esters for the dioxolane reagents.

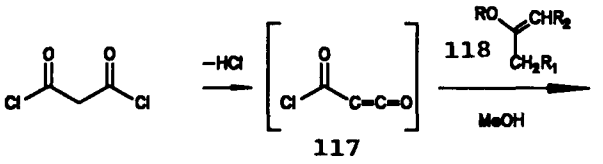


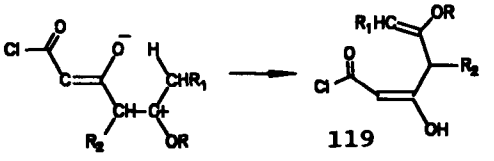
C. Acylation of Enolate Synthons

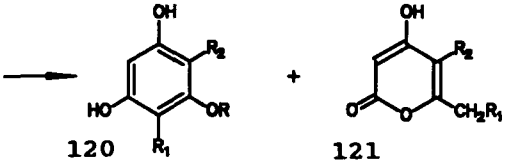
Several functionalities which are known to react similarly to enolates are capable of carbon acylation. The advantages which pertain to other enolate reactions also apply here, specifically, almost complete regioselectivity during the electrophilic attack, and the obviation of highly basic

conditions. The use of enamines in acylation reactions has already been addressed; the method is particularly well-suited for enone acylation, being notable for high reactivity and ease of workup.

Enol ethers are rapidly C-acylated at low temperature by acid chlorides. For example, 2-alkoxypropenes (118) react with malonyl dichloride in ether, resulting in acylation of the sp^2 carbon atom. The reaction is envisioned as proceeding via formation of the highly reactive chlorocarbonyl ketene 117 via loss of HCl from the diacid chloride. Subsequent treatment with methanol affords the intermediate keto esters 119, which cyclize to afford phloroglucinols 120 and/or pyranone derivatives 121. The pyranones are easily converted to phloroglucinols; thus, the method represents a high-yield synthesis of this compound class.[68]



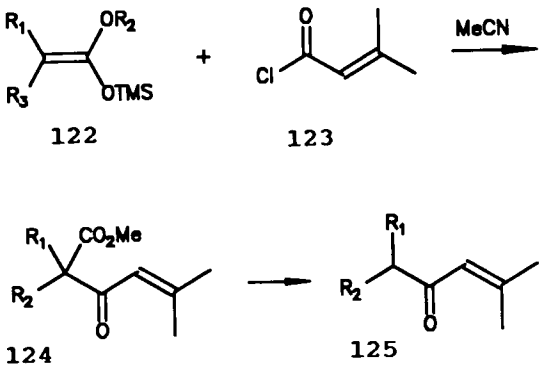




R	R_1	R_2	Yield of 120	Yield 121
Me	H	H	52%	43%
Me_2CH	H	H	43%	41%
Me	H	Et	80%	11%
Me	Me	Me	53%	30%

Another type of very highly reactive enolate equivalents is the ketene acetals, and they are quickly acylated by simple

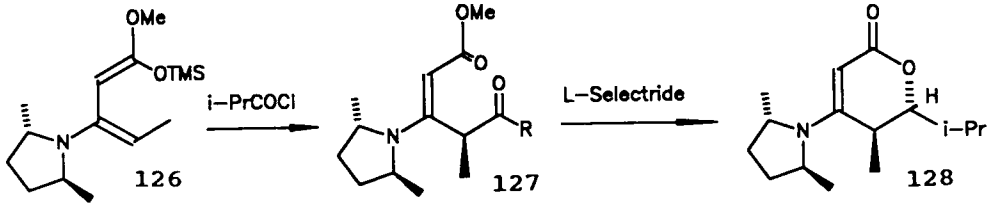
acid chlorides. Trimethylsilyl ketene acetals 122 react with 3-methylbutenoyl chloride (123) in acetonitrile to afford



R_1	R_2	R_3	Yield
C_5H_{11}	Me	H	70%
Me	Me	Me	70%
Ph	Et	H	30%
$-(CH_2)_2-$		H	80%

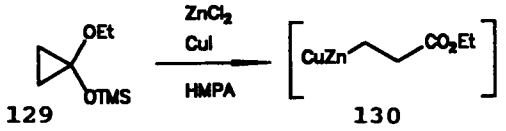
alkenyl ß-keto esters (e.g., 124) in good yield; these are easily decarboxylated to the isopropenyl alkyl ketones 125.[69] This sequence, which is also effective for 2-trimethylsilyl-oxy-4,5-dihydrofuran (i.e., a cyclic ketene acetal), was exploited in a synthesis of turmerone from 4-methyl-acetophenone.

An intriguing combination of ketene acetal and enamine acylation is demonstrated in the recently described threo-diastereoselective synthesis of lactones from vinylogous urethanes; the sequence is especially useful when a chiral auxilliary is employed.[70] Thus, isobutyryl chloride reacted



with the ketene acetal enamine 126, derived from the ester via treatment with LDA followed by chlorotrimethylsilane, to afford, the acyl enamine ester 127 which, after reduction with L-Selectride, provided the lactone 128 in enantiomeric excess of well over 90% in a yield of 89%.

Somewhat akin to ketene acetal chemistry is the utilization of 1-alkoxy-1-trimethylsilyloxycyclopropanes (129) as enolate synthons.[71] The unique feature of this method is the formation of a homoenolate equivalent 130 via treatment of 129 with zinc chloride in ether, followed by a catalytic



R	Yield
Ph	76%
$PhCH_2CH_2$	89%

quantity of copper bromide/dimethyl sulfide, and lastly with HMPA. Reaction of the homoenolate with acid chlorides,[72] including a nonaqueous workup, afforded the gamma-keto esters 131 in very good yield.

V. CONCLUSIONS

Obviously, much work has been done in the quest for methodology to effect the regioselective acylation of enolate anions and equivalent structures. House's landmark paper of 1966 accurately delineated the effects of the manipulation of reaction parameters on carbon/oxygen acylation ratios, and these data have been confirmed time and again. For many synthetic purposes, sufficient control can be exerted using these criteria. Unfortunately, the most important parameter,

as noted in this review, is usually the structure of the substrate itself; certain molecules seem destined to react at either oxygen or carbon despite all efforts to control the outcome otherwise. It is this fact which has prompted the development of the host of indirect methods outlined above. Synthetic research into more complex and structurally diverse molecules will assure a continuation of the ongoing search for control mechanisms which are specifically tailored for the application at hand.

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