Oxazoles in Carboxylate Protection and Activation

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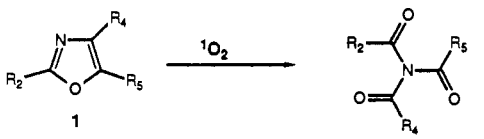
I. Introduction

The reactions of singlet oxygen with organic compounds have had many applications in synthesis.[1] These have been of special interest because of their selectivity, good yields, and the mild conditions employed. Among such oxidations have been the conversion of furans to unsaturated 1,4-dicarbonyl derivatives,[2] the α-oxygenation of carbonyl groups,[3] the hydroperoxidation of phenols,[4] allylic hydroperoxidation of substituted olefins through an ene reaction,[5] and the oxidative opening of imidazole rings.[6] One of the most promising of these singlet oxygen reactions in synthetic operations is the dye-sensitized photooxidation of oxazoles to triamides.[7] This transformation is remarkable in that the relatively stable oxazole ring undergoes rearrangement of the carbon–nitrogen skeleton in high yield to a triamide which may then serve as an excellent acylating agent. In this review, we will discuss the method for forming triamides from oxazoles and the use of substituted oxazoles as a source of activated carboxylates.

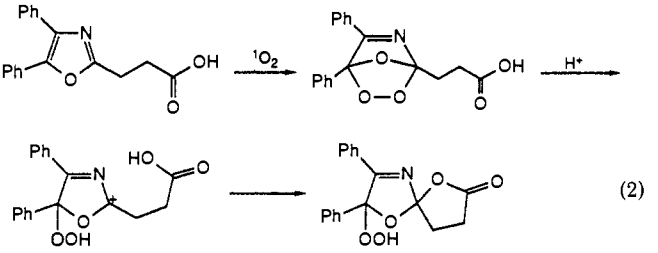
A. The Oxidative Rearrangement

The dye-sensitized photooxygenation of oxazoles of type 1 in solvents such as methanol, chloroform, or methylene chloride takes place rapidly and nearly quantitatively as outlined in eq 1. This transformation



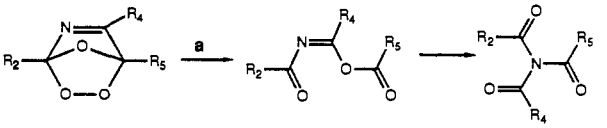
(1)

has been pictured in terms of a Diels–Alder-like uptake of singlet oxygen to form a 2,5-endoperoxide which is then converted by rearrangement to the triamide. Evidence for the mechanism of initial oxygen uptake has been obtained by oxygen-18 studies which clearly show that a 2,5-endoperoxide is formed rather than a 4,5-dioxetane.[8] In addition, the endoperoxide intermediate has been trapped by intramolecular nucleophilic attack of a carboxylate residue substituted at the 2-position as shown in eq 2.[9]



(2)

The mechanism by which the endoperoxide is converted to the triamide has not been conclusively established. Visualized in one reaction path, (a) the endoperoxide takes part in a Baeyer–Villiger-like rearrangement to an imino anhydride which then undergoes an *O*-acyl to *N*-acyl shift (eq 3). Evidence in support



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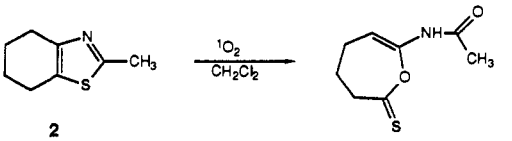
of this view has been found in the case of the photooxygenation of the thiazole derivative (**2**) where an in-



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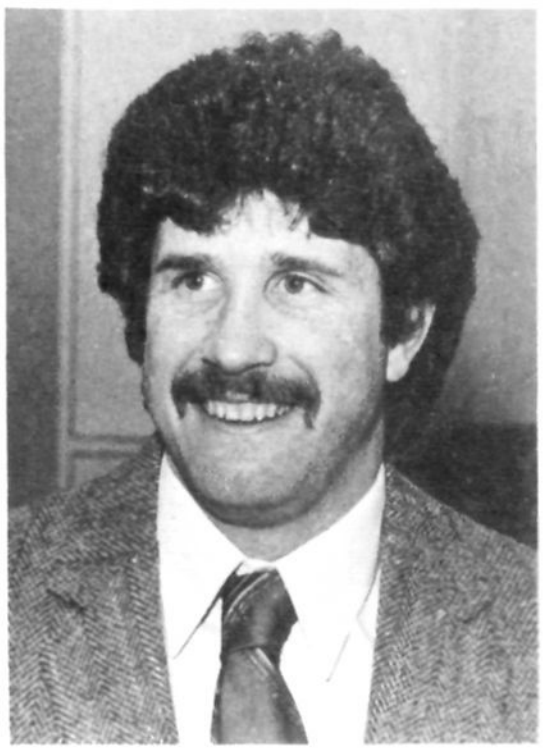
Harry Wasserman is Eugene Higgins Professor of Chemistry at Yale University. He received his B.S. degree in chemistry from M.I.T. and his Ph.D. from Harvard University. He served in the Army Air Force during World War II, and joined the faculty of Yale University in 1948. He has been chairman of the Chemistry Department and Director of the Division of Physical Sciences at Yale. In 1965, he served as chairman of the Organic Division of the ACS. Since 1960, he has been American Editor of *Tetrahedron Letters*. His research interests are in the development of new synthetic methods from reactive intermediates such as singlet oxygen and cyclopropanone, and in their application to the syntheses of natural products in the β-lactam, macrolide, and polyamine fields.

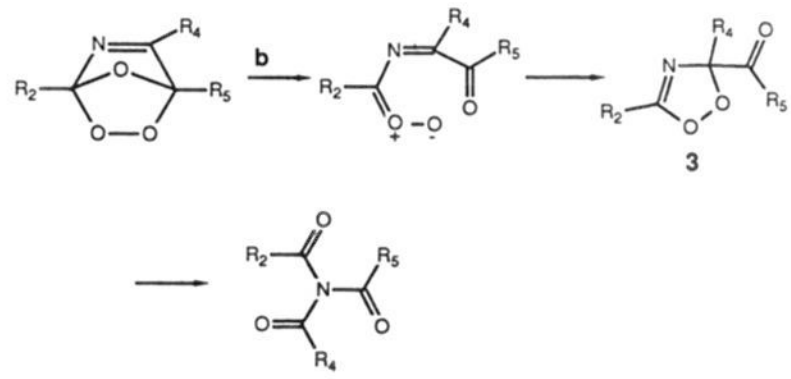


Keith McCarthy received his B.S. degree in 1980 from Colorado State University and his Ph.D. in 1985 from the University of California at Santa Barbara under the direction of Professor Bruce Lipshutz. He is currently an NIH postdoctoral fellow at Yale University, working with Professor Wasserman on the synthesis of erythrina and pyrrolizidine alkaloids.

termediate corresponding to an imino anhydride has been isolated.[10] On the other hand, the possibility exists, as in (b), that the endoperoxide, as a type of ozonide, could undergo initial rearrangement to a carbonyl oxide,[11] followed by an intramolecular addition of the peroxidic function to the α,β-unsaturated carbonyl group, generating a cyclic peroxide **3**. A product of this type has been reported by Scarpatti in the reaction of

K. Spencer Prowse received his B.S. degree in 1982 at Bates College and his M.S. in 1984 at Yale University, where he is currently completing his doctoral studies under the direction of Professor Wasserman. His doctoral work has focused on the use of the oxazole–triamide rearrangement in synthetic applications.

a methoxyoxazole with singlet oxygen.[12] The cyclic peroxide could then rearrange by a 1,2-acyl shift to give the triamide (eq 4). To date, there has been no definitive evidence to distinguish between these alternatives.



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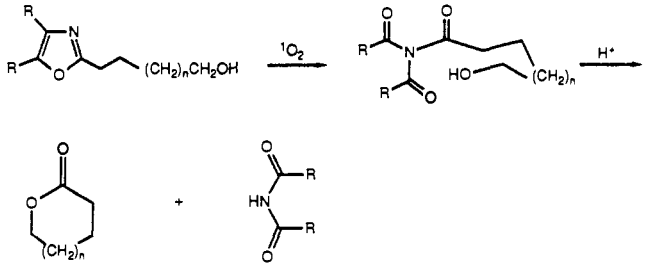
B. The Nature of the Carboxylate Activation

Transformation of the oxazole to a triamide by singlet oxygen effectively creates activated carboxylates at each of the three carbon atoms of the parent heterocyclic system. These electrophilic centers are targets for intermolecular or intramolecular attack by nucleophilic species. Utility of this process in formation of carboxyl derivatives would, of course, depend on the selectivity of attack at a specific carbonyl group. In this review, we will show how such selective attack can be accomplished by intramolecular acylation of an ω-hydroxyl group substituted at the 2-position of a 2-alkyl-4,5-diaryloxazole according to the general representation in Scheme I. We will also show that this intermolecular reaction takes place selectivity at the C_2–N carboxylate in oxazoles bearing a protected amino acid as part of a peptide side chains at the 2-position.[13] Furthermore, other studies on acylation by triamides containing mixed acyl and aroyl groups will be discussed.

SCHEME I



C. Description of the "Standard Photooxidation"[14]

The dye-sensitized photooxidation may be typically run in a photolysis vessel of approximately 100-mL capacity equipped with a side-arm for a condenser, a small sampling inlet fitted with a serum cap, a fritted glass disc of medium porosity through which oxygen is bubbled, and an immersion well permitting internal irradiation. The photolysis vessel and its condenser are attached to a manifold containing two three-way stopcocks. One stopcock is used as a vent in purging the system of air. The other stopcock, used to admit oxygen into the system, is also connected to a gas buret, permitting measurement of oxygen uptake.

The manifold may be connected to an air-circulating diaphragm pump by way of a shunt valve which permits the rate of oxygen uptake to be varied. The pump is used to purge the system of air prior to a reaction and to disperse oxygen in the reaction solution throughout the irradiation. For our studies, the light source was either a General Electric 200W Quartzline lamp or a Sylvania 650W DWY tungsten halogen lamp. The lamp was placed in the immersion well, cooled by running water, and normally operated at 75 to 110 volts.

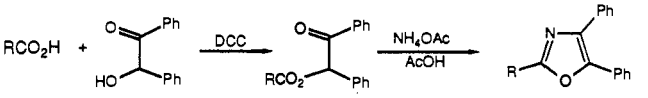
In a typical oxidation, ca. 0.1 M solution of the substrate containing the dye sensitizer (ca. 10 mg/1 g substrate) was added to a dry photolysis well. Dry oxygen was passed through the well in a closed system at room temperature while the reaction was irradiated with the tungsten–halogen lamp. The photooxygenation reaction was usually monitored by thin-layer chromatography until all the starting material was consumed.

II. Formation of Substituted Oxazole Substrates

In this section we will describe some of the methods for forming substituted oxazoles, giving special emphasis to the procedures which we have used in our synthesis of natural products and peptides. Turchi's review in this journal provides a more comprehensive coverage.[15]

The oxazole derivatives which were used in our synthetic applications were prepared in one of three ways: (a) direct ring synthesis of the heterocyclic system starting with benzoin and a suitable carboxylic acid,[16] (b) substitution of the alkyl group at the 2-position of an oxazole,[17] or (c) elaboration of a known oxazole via formation of an anion at the 2-, 4-, or 5-position followed by nucleophilic displacement reactions.[18]

SCHEME II



A. Direct Ring Synthesis

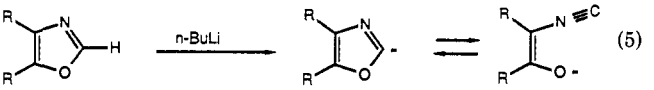
Formation of 4,5-diphenyloxazoles takes place readily by the standard Davidson procedure employing the carboxylic acid, benzoin, and DCC to form the keto ester (4) (Scheme II). This ester can then be converted to the corresponding oxazole with ammonium acetate in glacial acetic acid in overall yields of 80–85%. As will be outlined in the section on peptide synthesis, below, this reaction can be generally used to form oxazoles from protected amino acids. Alternatively, the oxazole may be prepared by treating benzoin with a suitable nitrile or a primary amide in H_2SO_4.[16b] Although this route requires one less step, it calls for an excess of the nitrile (or primary amide) which can be difficult to remove from the reaction mixture.

B. Substitution of the 2-Methylene Group

The activation of a 2-methylene group by the oxazole ring permits substitution at this site by electrophilic species. In general, the anion can be formed exclusively at this position by using LDA at −78 °C in THF and then allowed to react with an alkyl halide, an aldehyde, or an epoxide to provide the corresponding derivatives. As is outlined in the section on macrocyclic lactones, the electrophilic species may contain a suitably protected hydroxyl group which, at a later stage, can be deprotected for intramolecular acylation by the triamide. Tables I[17a] and II[17b] list some recent studies by two independent groups on the alkylation of oxazoles.

C. Direct Substitution of the Oxazole Ring

Substitution of an alkyl group at the 2-methylene position permits the use of an oxazole as an acetic acid equivalent as described above. To employ the oxazole system as a formate anion equivalent would require direct substitution at one of the ring carbon atoms. Kozikowski,[19] Schollkopf,[20] and Jacobi[21] have reported that the 2-position of the oxazole ring can be deprotonated using *n*-BuLi but there has been only sparse mention of the reactivity of this anion, possibly because ring opening can take place as a competing process to form the isonitrile as shown in eq 5.



(5)

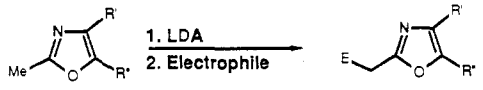
Employing the 4,5-diaryl oxazole (R = OCH_3)[16b] (Table III) as our substrate, we found that the 2-anion is formed quantitatively with *n*-BuLi at −78 °C. As expected, this 2-lithiooxazole reacts cleanly with aldehydes and ketones at −78 °C to form the substituted carbinols. Treatment of the anion with aliphatic nitriles apparently results only in proton abstraction (enolization) without addition to the nitrile, although use of benzonitrile did afford the ketone in excellent yield after hydrolysis. With primary halides, only low yields

TABLE I

alkyl iodide	% yield
CH_3I	73
$CH_3CH_2CH_2I$	82
$THPO(CH_2)_{11}I$	57[a]
$THPO(CH_2)_{12}I$	43[a]
$THPOCH(CH_3)(CH_2)_{11}I$	40[a]
$THPOCH(CH_3)CH_2CH{=}CH(CH_2)_5I$	43[a]

[a] Yield of alcohol after hydrolysis of THP ether.

TABLE II



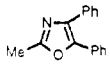
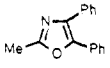
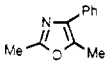
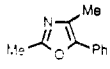
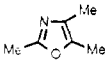
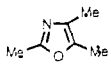
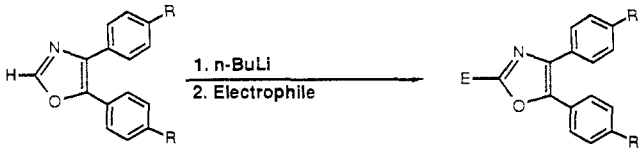
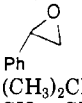
substrate	electrophile	% yield
	CH_3I	84
		90
	$CH_2{=}CHCH_2Br$	80
	$n\text{-}C_6H_{13}CHO$	80
		95
		72

TABLE III



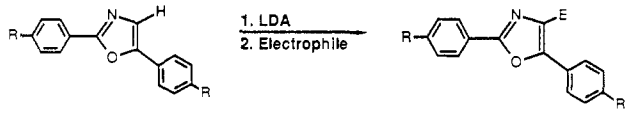
R	electrophile	% yield
H	D_2O	100
	Me_3SiCl	*a*
OCH_3		*c*
	$(CH_3)_2CHCHO$	70
	$CH_2{=}CHCHO$	83
	$PhCH_2Br$	27
	CH_3CH_2I	21
	$CH_3CH_2CH_2I$	23
	$PhCH_2CN$	*b*
	PhCN	85
	$ClCH_2CH_2CH_2CN$	*b*

[a] Reacts with the open form. [b] Only enolization observed. [c] No reaction.

of alkylated material could be obtained. Side products presumably arise via reaction with the ring-opened enolate.

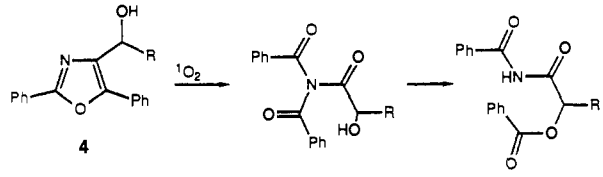
Attempts to metallate/alkylate the 4-position of the 2,5-diphenyloxazole were generally more successful. When *n*-BuLi was used to generate the anion, substantial butyl incorporation was observed at the 2-position by an addition/elimination sequence. On the other hand, LDA and KDA were effective in deprotonating the 4-position at −78 °C with no undesirable substitution. Once generated, the 4-lithio derivatives showed the expected reactivity with electrophiles such as aldehydes, ketones, and primary alkyl halides (Table IV). Acid chlorides reacted with 2 equiv of the oxazole anion to form the corresponding tertiary alcohols. Esters, imines, and epoxides were unreactive with or without Lewis Acid catalysis.[22] Attempts to metallate the 2,5-bis(p-methoxyphenyl)oxazole[23] led to somewhat discouraging results. As seen in Table IV, low yields of alkylated material was obtained as a result of competitive alkylation at the C-5 aryl substituent.

TABLE IV



R	electrophile	% yield
H	PhCHO	70
	$n\text{-}C_6H_3Br$	–
	Me_3SiCl	92
	$n\text{-}C_5H_{11}CHO$	82
	$(CH_3)_2CO$	80
	DMF	50
OCH_3	CH_3I	30
	CH_3CH_2I	20
	D_2O	50
	$(CH_3)_2CHCHO$	35
	$PhCH_2Br$	26

In all cases studied, photooxidation of the trisubstituted oxazoles proceeded smoothly and completely to afford the triamide. It is interesting to note that the triamides, derived from hydroxy oxazoles of type **4**, react readily in an intramolecular fashion to form the *O*-benzoylated imide in high yield (eq 6).



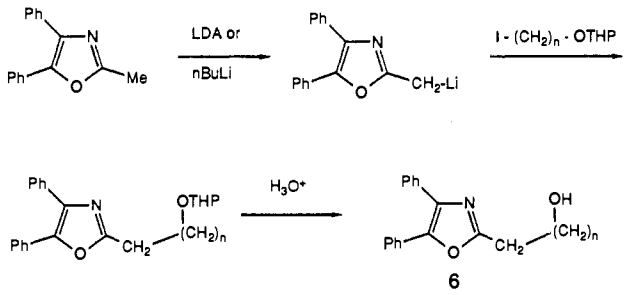
(6)

III. Synthesis of Macrocyclic Lactones Utilizing the Oxazole–Triamide Rearrangement

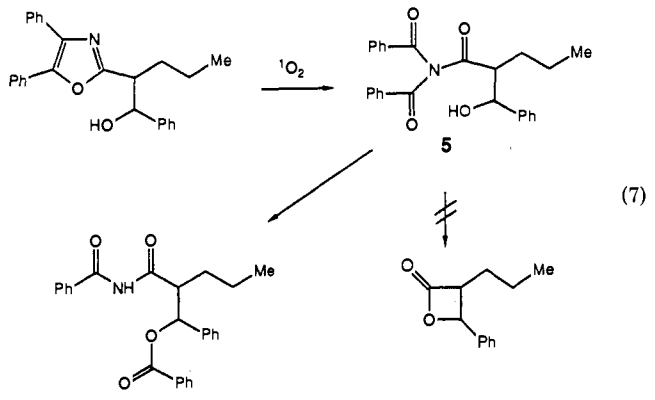
A. Introduction

As mentioned above, the conversion of oxazoles to triamides with singlet oxygen transforms each of the ring carbon atoms to a carboxylate derivative. For the purpose of lactone formation it would be desirable for an ω-hydroxyl group to react exclusively with the proximate carbonyl group (Scheme I). In practice, this acylation does take place preferentially, not only in the formation of five- and six-membered rings but also with larger systems. One exception to this rule is found in the case of the β-hydroxy derivative (**5**) where attack at the acyl carbonyl would lead to a β-lactone. In this circumstance, preference was shown for acylation by

SCHEME III



one of the aroyl carbonyls in a reaction proceeding through a six-membered transition state[24] (eq 7).



(7)

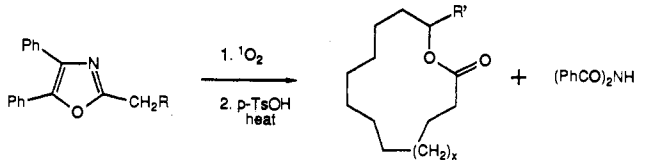
B. General Macrocyclic Lactone Synthesis

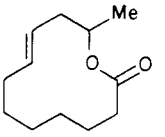
The intramolecular acylation of hydroxyl groups substituted on an oxazole of type **6** has been utilized as a general method for the formation of macrocyclic lactones.[7] Formation of the alcohol component generally takes place by treating the anion of an oxazole with an alkyl halide containing a suitably substituted hydroxyl group protected as the THP ether[7] (Scheme III). After deprotection of the alcohol in acid, the resulting hydroxy oxazole is allowed to react with singlet oxygen in the usual dye-sensitized photooxygenation. Formation of the triamide takes place in high yield, and this intermediate is then allowed to cyclize under conditions of acid catalysis and high dilution. Table V summarizes the synthesis of 13-tridecanolide (**7**),[25] 14-tetradecanolide (**8**),[26] (±)-14-pentadecanolide (**9**), and recifeiolide (**10**)[27] by this process.

C. Recifeiolide

A procedure for forming the substituted hydroxyl side chain and subsequent cyclization in the case of recifeiolide is outlined in Scheme IV. The readily available 2-methyl-4,5-diphenyloxazole[16] was metallated using LDA at −78 °C in THF. The anion was then alkylated with the acetal of 6-iodohexanal, followed by hydrolysis in acid. The newly formed oxazole–aldehyde (**11**) was subsequently treated with the ylide alkoxide (**12**)[28] in a Wittig reaction to generate the required unsaturated residue (**13**). Dye-sensitized photooxygenation under the standard conditions liberated the reactive triamide (**14**) which was then cyclized with *p*-TsOH as catalyst. This sequence afforded a mixture of (*E*)- and (*Z*)-

TABLE V



R	lactone	% yield
$-(CH_2)_{11}OH$	**7**; $x = 2$, R′ = H	75
$-(CH_2)_{12}OH$	**8**; $x = 3$, R′ = H	76
$-(CH_2)_{11}CH(CH_3)OH$	**9**; $x = 3$, R′ = Me	64
$-(CH_2)_5CH{=}CHCH_2CH(CH_3)OH$		55

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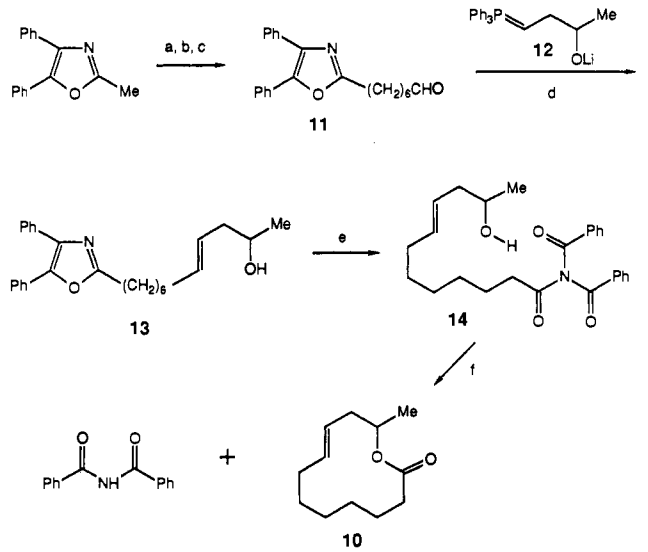
SCHEME IV[a]



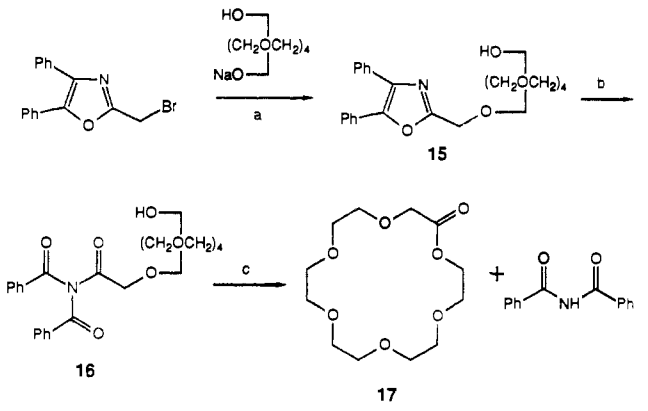
[a] (a) LDA, THF, −78 °C; (b) $I(CH_2)_5CH(OCH_2)_2$; (c) H_3O^+ (62% from methyloxazole); (d) 52%; (e) $^1O_2$, Sensitox, $CHCl_3$; (f) *p*-TsOH, benzene, reflux (55%).

(±)-recifeiolide (**10**)[29] from which the pure *E* form was isolated by chromatography.[30]

D. Polyether Lactones

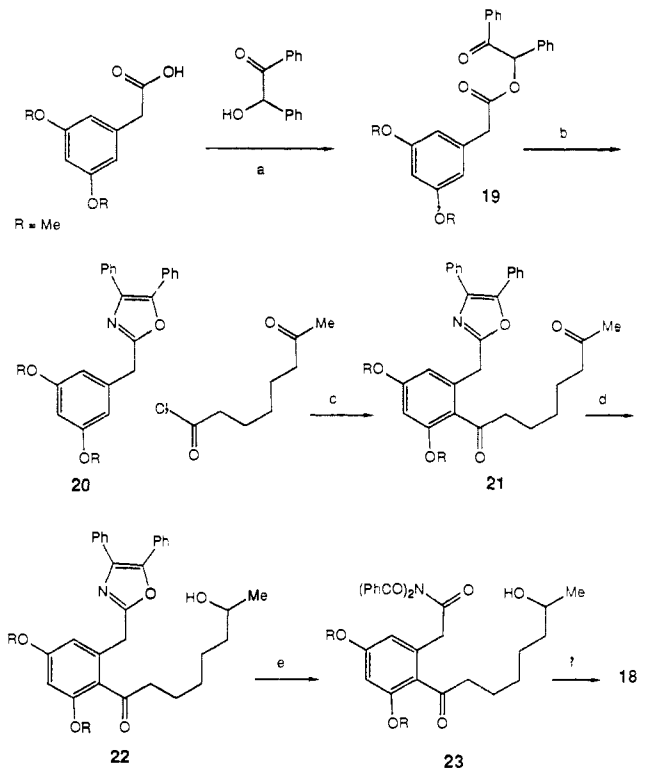
The oxazole–triamide rearrangement was found to be a useful reaction in the formation of polyether lactones because of the ease of attaching the polyether framework to the oxazole template. In this application, the 2-position of 2-methyl-4,5-diphenyloxazole was brominated (NBS) and the resulting halide displaced by the monosodium salts of polyethylene glycols. Thus 2-bromomethyl-4,5-diphenyloxazole,[31] acting in the capacity of a latent activated bromoacetic acid equivalent, was converted as shown in Scheme V to the desired ω-hydroxy polyether (**15**). Photooxygenation to the triamide (**16**) followed by acid-catalyzed cyclization in refluxing benzene gave 2-oxo-18-crown-6 (**17**). While under these conditions the cyclization step formed the lactone in only moderate yield (46%), Okahara has shown[32] that cationic binding, favored by the presence of the polyether network, helps to improve the yields of lactone formation in such cases.

SCHEME V[a]



[a] (a) NaI, dioxane (61%); (b) $^1O_2$, Sensitox, $CHCl_3$; (c) *p*-TsOH, benzene (46%).

SCHEME VI[a]



[a] (a) DCC, DMAP, Et_2O (82%); (b) NH_4OAc, HOAc (83%); (c) $AlCl_3$, CS_2 (50%); (d) $NaBH_4$, EtOH, H_2O (94%); (e) $^1O_2$, Sensitox, CH_2Cl_2; (f) *p*-TsOH, benzene, heat (31%).

E. Synthesis of (±)-Di-*O*-Methylcurvularin

Synthesis of the curvularin system was carried out effectively using the oxazole triamide method of activating the carboxyl group. This synthesis is of special significance in that earlier workers were unable to form this 12-membered aromatic lactone by ring closure from the corresponding hydroxy acid.[33,34,35] Successful syntheses of curvularin derivatives were achieved only by intramolecular Friedel–Crafts acylation (Figure 1). Earlier unsuccessful attempts for intramolecular ester formation utilized DCC,[33] trifluoroacetic anhydride,[33] the 2-pyridylthiol ester method with[34] or without[35] silver perchlorate, and the *tert*-butylthiol ester procedure.[35]

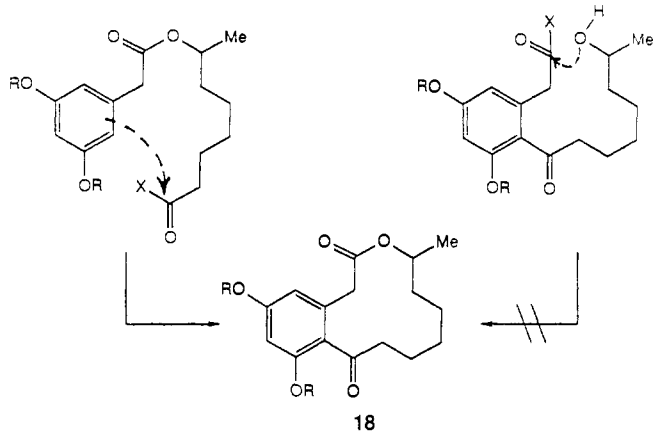


Figure 1.

Our successful completion of this synthetic objective by oxazole–triamide carboxylate activation is outlined in Scheme VI.[7]

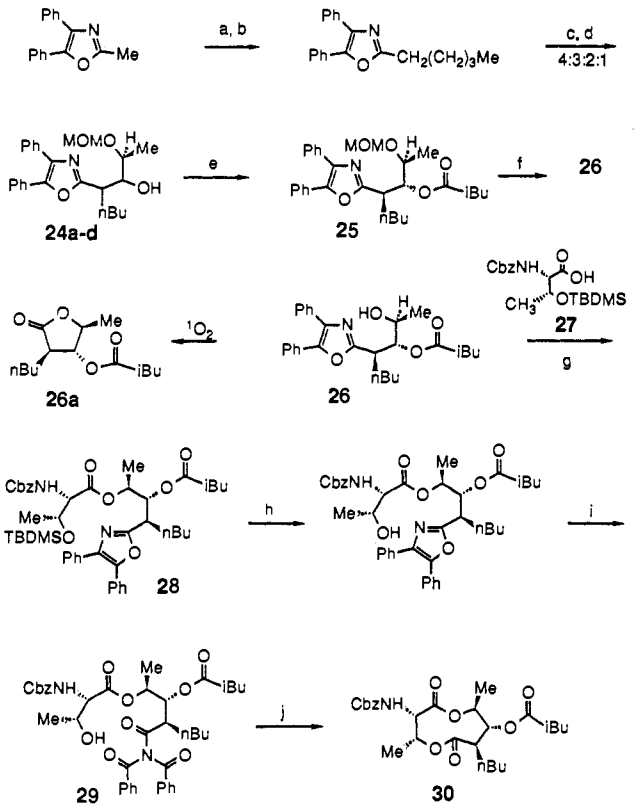
To form (±)-di-*O*-methylcurvularin (**18**), the oxazole functionality was built into the aromatic portion of the curvularin system[36] by DCC coupling of 3,5-dimethoxyphenyl acetic acid with benzoin in the presence of DMAP[37] yielding the ester (**19**), which was then treated with excess ammonium acetate in refluxing HOAc to produce the desired oxazole (**20**). Friedel–Crafts acylation[38] of **20** with 7-oxooctanoyl chloride provided the diketooxazole (**21**) which underwent selective reduction of the aliphatic carbonyl group with $NaBH_4$,[39] generating **22**. The hydroxy oxazole (**22**) was then converted by dye-sensitized photooxygenation (Sensitox) to the corresponding triamide (**23**) which underwent acid-catalyzed cyclization to yield (±)-di-*O*-methylcurvularin (**18**).

F. Antimycin A_3

In the synthesis of Antimycin A_3, the protecting and activating functions of the oxazole were demonstrated in striking fashion.[40] Starting the 2-methyl-4,5-diphenyloxazole as a template, the complete carbon–oxygen framework was built up in a varied sequence of steps which allowed the carboxyl to remain in latent form until the penultimate step in which it is unmasked by photooxidation. As outlined in Scheme VII, alkylation at the 2-position using butyllithium/butyl iodide was followed by a second reaction at the 2-position with optionally active (*S*)-2-[(methoxymethyl)oxy]propanal,[41] to give a mixture of four diastereomers (4:3:2:1) (**24a–d**). The diastereomeric mixture was acylated with isovaleryl chloride in pyridine and the major component (**25a**) of the diastereomeric mixture separated. Deprotection of the MOM group with boron trifluoride etherate and thiophenol[42] afforded the hydroxy alcohol (**26**). At this stage of the synthesis the absolute stereochemistry could be established by converting **26** to (+)-blastmycinone (**26a**),[43] a product of mild saponification of antimycin A_3.[44] This was accomplished by photooxygenation of **26** (Sensitox, CH_2Cl_2, 25 °C, 3 h) forming the triamide which spontaneously cyclized to the lactone **26a** (35%).[40]

Condensation of **26** with the *N*-carbobenzoxy-L-threonine derivative (**27**)[45] (DCC, DMAP, CH_2Cl_2) gave

SCHEME VII[a]



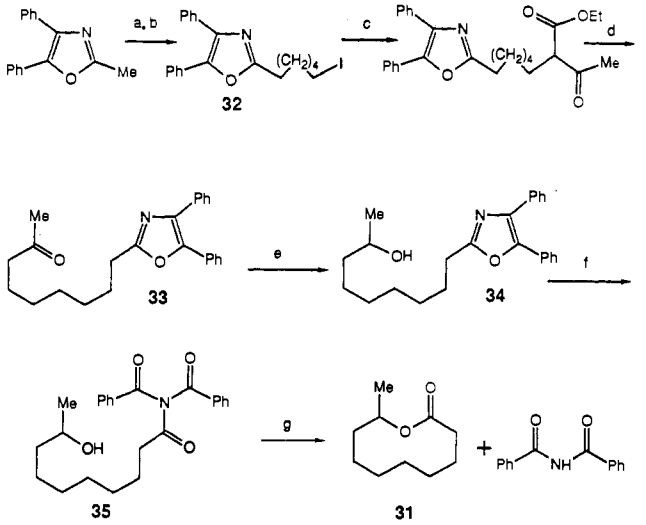
[a] (a) LDA, THF, -78 °C; (b) $CH_3(CH_2)_3I$ (93%); (c) *n*-BuLi, -78 °C; (d) (*S*)-2-[(methoxymethyl)oxy]propanal (58%); (e) ClCO-*i*-Bu, pyridine (74%); (f) BF_3OEt_2, PhSH, CH_2Cl_2 (57%); (g) DCC, DMAP, CH_2Cl_2 (95%); (h) *n*-Bu_4NF, THF, 0 °C (64%); (2) $^1O_2$, Sensitox, CH_2Cl_2; (j) *p*-TsOH-Py, xylenes, heat (20%).

the acyclic ester precursor (**28**). Fluoride deprotection of the *tert*-butyldimethylsilyl group followed by dye-sensitized photooxygenation led cleanly to the activated triamide (**29**). Compound **29** was dissolved in xylene and added slowly to a solution of pyridinium *p*-toluene sulfonate in refluxing xylenes in a modified high dilution technique. Under these buffered acid catalysis conditions the desired nine-membered dilactone (**30**) was formed. This dilactone had previously been converted to antimycin A_3 by Kinoshita and co-workers.[46]

G. Intermediate Sized Lactones, Phoracantholide I

Earlier work demonstrated that the formation of small and large ring lactones takes place readily through intramolecular acylation of triamide by ω-substituted hydroxy groups.[7,40] More recently it has been shown that the cyclization of a hydroxy triamide is a promising method of forming medium-ring lactones as exemplified by the synthesis of the 10-membered plant product, phoracantholide I (**31**).[47] The procedure for its formation follows the lines developed earlier and is outlined in Scheme VIII. As in the case of antimycin A_3, the cyclic skeleton was built up from the 2-methyl-4,5-diphenyloxazole template. Monoalkylation of 1,5-diiodopentane with the anion of 2-methyl-4,5-diphenyloxazole yielded the aliphatic iodooxazole (**32**). The remainder of the framework was formed by displacing the halide with the sodium anion of ethyl acetoacetate, saponification, and decarboxylation

SCHEME VIII[a]



[a] (a) LDA, THF, -78 °C; (b) THF, $I(CH_2)_5I$ (60%); (c) $EtOCOCH_2COCH_3$, NaH, THF (71%); (d) 10% NaOH:THF/10:3 (92%); (e) NaOH (quant); (f) $^1O_2$, Sensitox, CH_2Cl_2; (g) *p*-TsOH-Py, xylenes heat (25%).

(NaOH, THF) to give the keto oxazole (**33**) which could be reduced by $NaBH_4$ to the hydroxy oxazole (**34**). Dye-sensitized photooxidation (Sensitox, CH_2Cl_2) transformed the oxazole to the triamide (**35**), which upon exposure to the normal cyclization conditions gave the 9-decanolide, phoracantholide I (**31**).[48,49]

H. Double Activation in the Formation of Macrocyclic Lactones

The success achieved in the formation of macrocyclic lactones using triamides as acylating agents suggests that these species may play a special role in a so-called double activation process. In the acylation pictured below, attack of the hydroxyl group on the protonated triamide leads to an enolate-like anion capable of assisting in the removal of the hydroxy proton through a six-membered transition state (Figure 2).[7] Other examples of double activation have been reported[50] using 2-pyridinethiol among other species. An entropic advantage in the triamide acylation may well like in the fact that there are two aroyl residues which can participate in the step involving proton removal.

IV. Oxazoles as Protected Carboxylates In Peptide Synthesis

The use of an oxazole as a source of a latent carboxy group offers special advantages in peptide synthesis. The oxazole is relatively resistant to many of the operations involved during the introduction or removal of protecting groups in the amide-forming process, since it is resistant to many of the conditions of hydrolysis in acid and base. Furthermore, the strong ultraviolet activity of the oxazole moiety facilitates the identification and purification of oxazole-containing intermediates. Unlike other activated carboxyl components, oxazoles are stable to amino groups and can be prepared and stored in bulk. In addition, their solubility in organic solvents makes them more easily handled. Finally, and of particular significance, the carboxy group

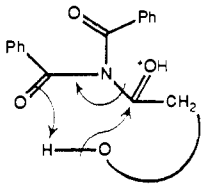
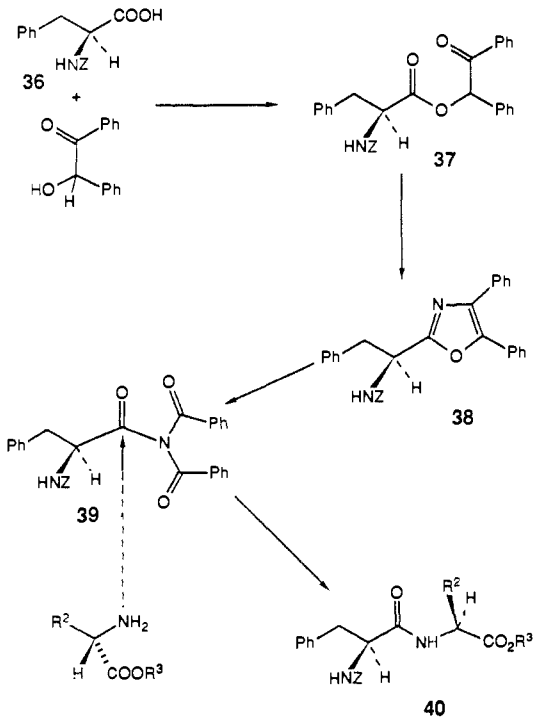


Figure 2.

SCHEME IX

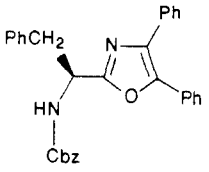
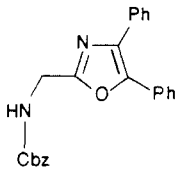


can be liberated in activated form from its protected state in nearly quantitative yield under mild conditions for reaction with nucleophilic species.

The oxazole–triamide procedure employed for converting *N*-protected amino acids to dipeptides is shown in Scheme IX.[13] The free carboxyl group of *N*-(carbobenzoxy)-*L*-phenylalanine (**36**) was converted to the oxazole by first coupling it with (±)-benzoin to give the benzoin ester (**37**). Following normal workup, the crude ester was treated with ammonium acetate in glacial acetic acid to afford 2-[1-(*N*-(carbobenzoxy)amino)-2-phenylethyl]-4,5-diphenyloxazole (**38**). Formation of the dipeptide was accomplished by photooxygenation of the substituted oxazole in *dry* CH_2Cl_2 (methylene blue sensitizer) to yield the triamide (**39**). Treatment of **39** with an appropriate amino acid derivative in DMF gave the dipeptide (**40**).

Table VI lists the dipeptides formed in this manner. In general, DMF appears to be the solvent of choice for the coupling reaction, providing products 40–50% higher in yield than with pyridine, acetonitrile, or chlorinated solvents.[51] One exception was found when an amino acid ester was used as the nucleophile, in which case the coupling proceeded smoothly in dry dichloromethane. The procedure is amenable to the preparation of optically pure dipeptides since the optical integrity of the α-position in the *N*-protected amino acid is not compromised during the sequence depicted in Scheme IX.[51]

TABLE VI

protected amino oxazole	amino acid or ester	dipeptide[a]	yield, %
	$H_2NCH(CH_3)$-COOH	Cbz-Phe-Ala-OH	64
	$H_2NCH(CH_3)$-COOEt	Cbz-Phe-Ala-OEt	85
	$(CH_3)_2CHCH_2$-$CH(NH_2)$-COOH	Cbz-Phe-Leu-OH	64
	H_2NCH_2COOH	Cbz-Gly-OH	52
	$PhCH_2CH$-$(NH_2)COOH$	Cbz-Gly-Phe-OH	71

[a] All amino acids have the L-configuration.

Hydroylsis or alcoholysis of triamides generally requires acid catalysis, long reaction times (e.g., 24 h), and high temperature. By contrast, the triamides derived from acylaminooxazoles seem to have enhanced reactivity. Care must be taken to prevent moisture from entering the reaction media, as hydrolysis of the triamide to form the corresponding amino acid is a facile reaction. Furthermore one observes exclusive nucleophilic attack at the carbonyl bearing the α-amino substituent. Examples wherein a desamino triamide is employed as the acylating reagent affords a mixture of acyl and aroyl addition (see section on selectivity of acylation). The role of the protected amine substituent is not clear at this time; however, the inductive effect of this group may account for these observations. This method has been extended to the synthesis of tripeptide; however, racemic material is obtained, possibly viz azalactone formation (with accompanying racemization), which poses a limitation beyond the dipeptide stage (Figure 3).

The presence of groups such as indoles, sulfur-containing compounds, and imidazoles which are sensitive to singlet oxygen may pose some limitations on the use of oxazoles in these photooxidative processes. In practice, however, the oxazole ring reacts much more rapidly than indoles,[52] and imidazoles may be rendered relatively unreactive by acylation of the ring nitrogen atoms. (See section on β values). The successful syntheses of macrolides outlined earlier by photooxidation–cyclization renders this method potentially attractive for the preparation of cyclic peptides and cyclodepsipeptides.[53]

V. Other Applications

The use of the oxazole moiety as a latent carboxylate in the synthesis of optically active materials has recently been demonstrated by Pridgen and co-workers.[54] This work centers on the reactions of the chiral epoxy ester (**41**), a valuable intermediate in the synthesis of leukotrienes A–E,[55] starting with 2-methyl-4,5-diphenyloxazole shown in Scheme X.

Oxazole **16** was metallated under standard conditions and alkylated with the bromoacetal to give **42**. The

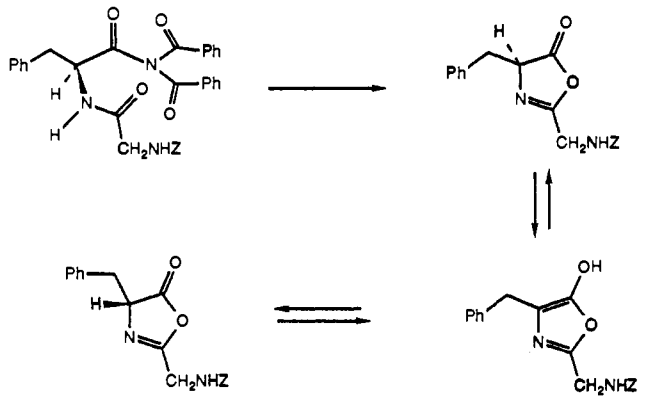
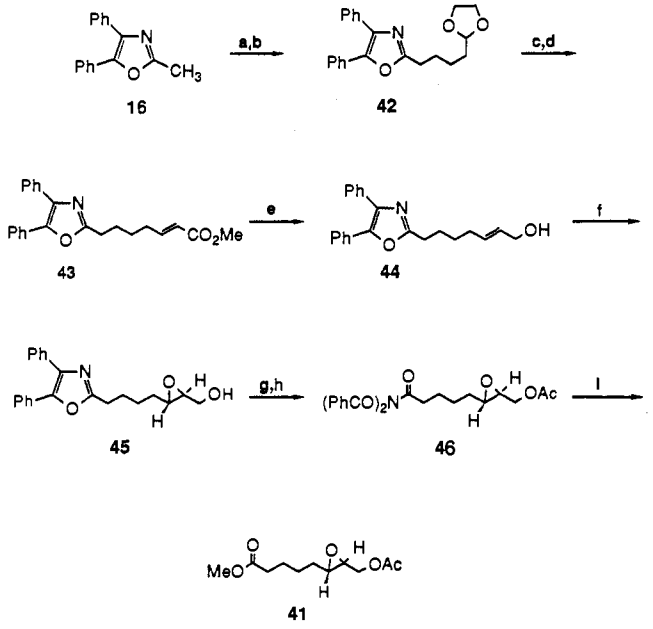


Figure 3.

SCHEME X[a]



[a] (a) *n*-BuLi, -90 °C; (b) $ICH_2CH_2CH_2CH(OR)_2$ (84%); (c) AcOH, H_2O (78%); (d) $Ph_3P{=}CHCO_2Me$ (95%); (e) DIBAL (68%) (f) (+)-DET, Ti(*i*-OPr)$_4$, TBHP (66%) (g) Ac_2O, Py (95%); (h) $^1O_2$, MeOH; (i) MeOH, TsOH, benzene (78%).

acetal was converted to the unsaturated ester via hydrolysis (AcOH, H_2O) and Wittig olefination of the resultant aldehyde to give the *E* isomer in excellent yield. DIBAL reduction afforded the allylic alcohol (**44**) which was cleanly converted to the optically pure epoxy alcohol (**45**) under Sharpless conditions.[56] Previous reports indicated that a terminal methyl or *tert*-butyl ester in a similar allylic alcohol interferes with the course of the epoxidation.[54] In earlier work addressing this problem Corey masked the terminal ester in the form of an olefin.[57] Although this expedient overcame the epoxidation obstacle, the number of additional steps required in the synthesis made this alternative somewhat unattractive. The primary alcohol (**45**) was acylated (Ac_2O, pyr) and the oxazole converted to the triamide (**46**) by photooxidation. Methanolysis (TsOH, MeOH) then afforded the target ester (**41**). As expected, the acetate did not undergo methanolysis under these conditions in competition with the more highly reactive triamide.

VI. Selectivity of Nucleophilic Addition to the Triamide

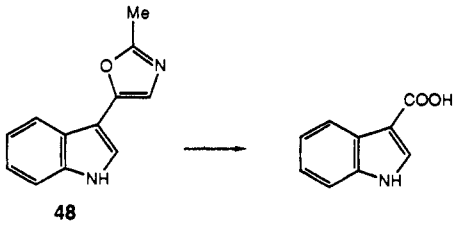
As outlined above, the addition of singlet oxygen to the oxazole generates a triamide in which the three carbonyls may each suffer attack by a suitable nucleophile. In intramolecular reactions, exemplified by lactone formation, and in the peptide syntheses outlined above, notable selectivity was observed in the nearly complete preference for acyl vs aroyl attack. In order to learn more about elements controlling selectivity in intermolecular reactions, we studied some of the electronic and steric factors involved.[18]

Initially the triamide formed from 2-alkyl-4,5-diphenyloxazole was investigated. Table VII outlines results obtained in reactions of a variety of nucleophiles with the triamides (**47a–d**) derived from alkyldiaryloxazole. In these intermolecular reactions we found no selectivity of addition. Attack at the acyl vs. the aroyl carbonyls took place in approximately a 1:1 ratio. When the size of the alkyl group was increased, the ratio of aroyl product rose to ca. 1.5:1.

Some selectivity in favor of the acyl carbonyl was observed when the aryl substituents contained p-methoxyl groups. As shown in Table VII, the reactions with nucleophiles favored acyl attack in ratios varying from 2:1 to 50:1. Additionally, we found that an increase in base strength of the attacking nucleophilic species resulted in enhanced reactivity at the acyl site. For example, using an alkoxide ($PhCH_2ONa$) for the reaction with the triamide (**47c**), acyl attack predominated 8:1 over aroyl reaction. Further evidence for the operation of this effect is found in the reaction of benzyl amine with the triamide. With the neutral amine, acyl to aroyl reaction took place in a ratio of ca. 3:1, whereas benzyl amide anion afforded greater than a 50:1 ratio. Further studies are needed on steric and electronic effects in the competitive acylation.

VII. β Values

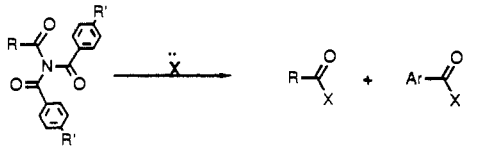
When designing a synthesis in which an oxazole is to be unmasked by dye-sensitized photooxidation to an activated carboxylate, an important factor to consider is the potential reactivity toward singlet oxygen of other functional groups within the system. For example, it is well known that indoles are reactive toward singlet oxygen.[58,59] However, in early work by Wasserman and Floyd[52] on the autoxidation of pimprinine (**48**) (eq 8)



(8)

it was found that the indole ring remained unreacted under conditions which completely consumed the oxazole. An excellent measure of substrate reactivity toward singlet oxygen is its β value, a concept first introduced by Foote et al.[60] This value is derived from a kinetic treatment of the dye-sensitized photooxygenation reaction process and is defined as the ratio

TABLE VII



entry	R	R′	nucleophile	ratio[a]	% yield[b]
47a	CH_3	H	LiOH, THF, H_2O	*c*	85
			$PhCH_2OH$, TsOH	1:1	
			$PhCH_2NH_2$	1:1	
47b	n-C_7H_{15}	H	LiOH, THF, H_2O	*c*	85
			$PhCH_2NH_2$	1:1.5	70
47c	CH_3	OCH_3	$PhCH_2OH$, TsOH	2:1	92
			$PhCH_2OH$, Et_3N	2:1	90
			$PhCH_2OH$, NaH	8:1	91
			PhMgBr	*d*	
			$PhCH_2OH$, CH_3MgBr	4:1	83
			$PhCH_2NH_2$	3.5:1	89
			$PhCH_2NH_2$, n-BuLi	>50:1	94
47d	C_2H_5	OCH_3	$PhCH_2OH$, NaH	6:1	92
			$PhCH_2NH_2$	1:1	91
			$PhCH_2NH_2$, n-BuLi	>25:1	80

[a] Refers to ratio of acyl attack to aroyl attack. [b] Combined yield. [c] Complete hydrolysis of the triamide. [d] No ratio obtained.

of the rate of decay of $^1O_2$ to $^3O_2$ over the rate of reaction of $^1O_2$ with substrate A (eq 9).[61]

$$^3O_2 \underset{k_d}{\rightleftharpoons} {}^1O_2 \xrightarrow[k_A]{A} AO_2$$

$$\frac{k_d}{k_A} = \beta \qquad (9)$$

According to the relationship described in eq 9, the smaller the relative value of β, in a given solvent,[62] the more reactive the substrate. The β values for various oxazoles, determined by Wasserman, Vinick, and Pickett,[63,64] have been shown to vary with solvent and substitution within the range of 1.5–18 × 10^{-3} M. Systems with β values within this range will be expected to undergo competitive oxidation with singlet oxygen. For example, as shown in Table VIII,[67] photooxidation of the oxazole would not be likely to suffer competition by groups such as thiophenes, and most alkenes such as 2-butene, isobutylene, α-pinene, and *cis*-4-methyl-2-pentene. Groups such as furan, pyrrole, and cyclopentadiene with β values in the same general range could be oxidized along with the oxazole.

VIII. Future Work: Coupling Oxazole Oxidation with Other Singlet Oxygen Reactions

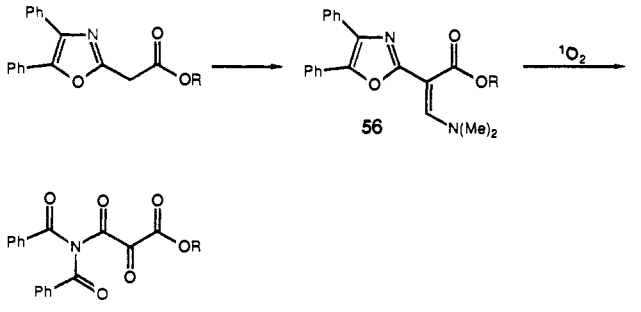
One aspect of the oxazole–triamide rearrangement which deserves further study involves the possibility for multiple oxidations in systems containing more than one singlet oxygen sensitive grouping. Thus, to cite one example, one can visualize the formation of special functional group aggregates, such as activated vicinal tricarbonyl systems. Cleavage of the enamino group by singlet oxygen concurrent with the oxazole oxidation of derivative **56** would generate this reactive assembly which has found recent use in carbacepham, carbapenam, and penem synthesis (Scheme XI).[68,69,70]

TABLE VIII

compd	β ($\times 10^3$ M) (rose bengal, MeOH)
tetramethylethylene	2.3[a]
2-methyl-2-pentene	150.0[a]
cis-4-methyl-2-pentene	8000.0[a]
2,5-dimethylfuran	0.28[a]
furan	4.5[b]
cyclopentadiene	4.4[b]
cyclohexadiene	45.0[b]
α-pinene	5000.0[b]
isobutylene	1600.0[b]
2-butene	12500.0[b]
furfurylamine	9.0[b]
2,5-dimethylpyrrole	160.0[b]
thiophene	>600000.0[b]
triphenylphosphine	5.0[b]
diethyl sulfide	25.0[b]
4-methyl-2,5-diphenyloxazole	5.77[c]
2-(*m*-chlorophenyl)-4-methyl-5-phenyloxazole	11.0[c]
2-(*p*-nitrophenyl)-4-methyl-5-phenyloxazole	16.6[c]
2-(*p*-methoxyphenyl)-4-methyl-5-phenyloxazole	3.8[c]

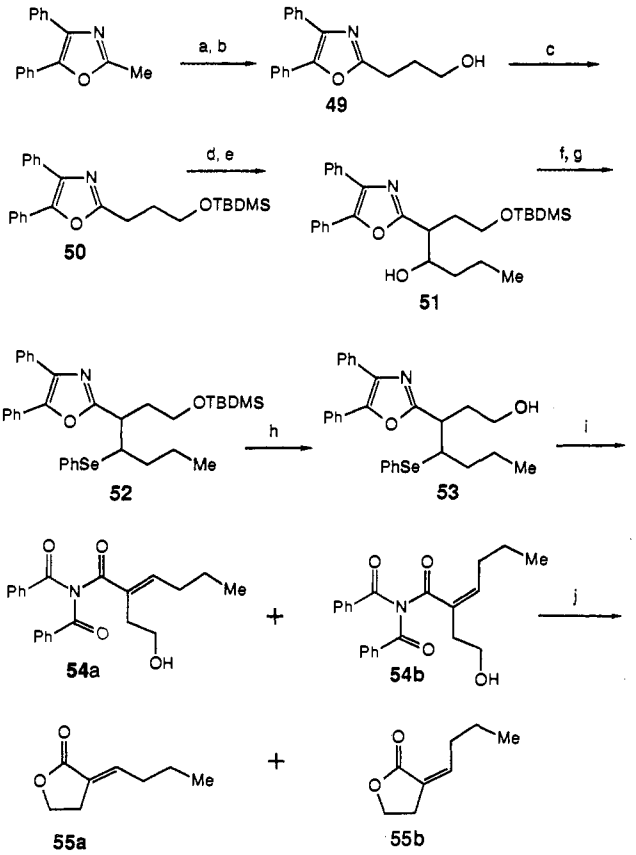
[a] Reference 65. [b] Reference 66. [c] Reference 63. [d] Reference 64.

SCHEME XI



In this connection, the most recent work on the oxazole–triamide rearrangement by Wasserman and Lu[51] has used a two-center oxidation of a suitably substituted oxazole for the formation of α,β-unsaturated lactones. Here, an adventitiously placed selenide is oxidized to a selenoxide along with the conversion of the oxazole

SCHEME XII[a]



[a] (a) LDA, THF, −78 °C; (b) $O(CH_2)_2$, HMPA (85%); (c) TBDMSCl, Et_3N (99%); (d) LDA, THF, −78 °C; (e) $CH_3(CH_2)_2CHO$ (75%); (f) MsCl, Et_3N, CH_2Cl_2; (g) PhSeSePh, $NaBH_4$, EtOH (82%); (h) HOAc:THF:H_2O/3:1:1 (98%); (i) $^1O_2$, TPP, $CHCl_3$; (j) $CHCl_3$, *p*-TsOH, reflux (91%).

to triamide. Elimination of the selenoxide takes place readily so that the α,β-unsaturated triamide can then be cyclized to form the α,β-unsaturated lactones, systems of special biological interest (Scheme XII).

To form the starting material for this two center reaction, the anion of 2-methyl-4,5-diphenyloxazole was reacted with ethylene oxide in the presence of HMPA to afford the hydroxy derivative (**49**). After protection of the hydroxyl group with *tert*-butyldimethylsilyl chloride, the silyloxy oxazole (**50**) was treated sequentially with LDA and butyraldehyde to yield the hydroxy silyloxy oxazole (**51**) as a pair of diastereomers. The hydroxyl group was converted to the mesylate[71] and then to the phenylselenenyl derivative (**52**) by refluxing the mesylate in an oxygen-free ethanol solution containing PhSeSePH and $NaBH_4$. Removal of the silyl protecting group (HOAc, THF, H_2O 3:1:1) yielded the mixture of phenylselenenyl hydroxy oxazoles (**53**) which were converted by photooxidation to the *E* and *Z* unsaturated triamides (**54a, b**). These then yielded the *E* and *Z* α-alkylidene lactones (**55a, b**) (ca. 1:1) when heated to reflux in $CHCl_3$ with a catalytic amount of *p*-TsOH.

Registry No. Oxazole, 288-42-6.

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