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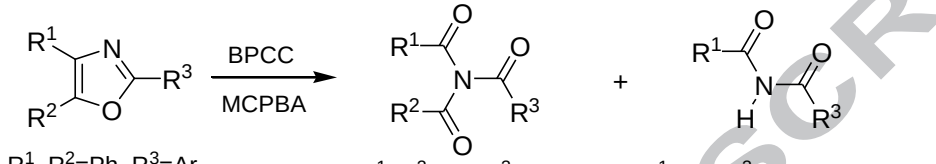

R^1, R^2=Ph, R^3=Ar, alkyl, cycloalkyl

R^1, R^2=Ph, R^3=Ar (62-71%)

R^1=Ph, R^3=alkyl, cycloalkyl (38-60%)

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m-Chloroperbenzoic acid-oxchromium (VI)-mediated cleavage of 2,4,5-trisubstituted oxazoles

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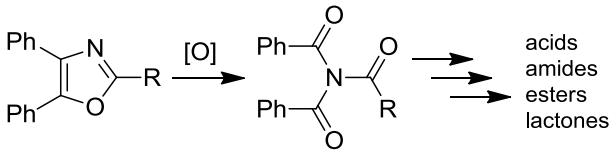
ABSTRACT

An array of 2-substituted-4,5-diphenyloxazoles were found to be cleaved to triacylamines and diacylamines (imides) using a reagent system composed of 3-chloroperbenzoic acid (MCPBA) and 2,2'-bipyridinium chlorochromate (BPCC). The 2-alkyl-4,5-diphenyloxazoles give imides (38-60%) as the predominant cleavage product while the 2-aryl-4,5-diphenyloxazoles give triacylamines (44-71%). Two mechanisms involving intermediates such as cyclic endoperoxides or oxachromacycles were proposed. An application of the oxidative cleavage to the multi-step synthesis of (±)-phoracantholide I *seco* acid is detailed.

1. Introduction

In principle, an entire natural product synthesis may be designed around the 2-substituted 4,5-diaryloxazole framework whereby the oxazole functions as a masked carboxylic acid component. The oxazole synthons can be elaborated through nucleophilic or electrophilic reactions and these reactions can be of sufficient mildness or robustness to allow application at either the beginning or end of the synthesis.[1,2] Once the unmasking or otherwise deprotection of the carboxylic acid moiety is warranted, a number of options should be available to accommodate formation and isolation of a potentially sensitive product. A prime example of all the above points is the utilization of the 4,5-diaryloxazole framework in the total synthesis of oasomycin as reported by the Evans group.[3] The oxazole, functioning as a masked carboxylic acid equivalent, was brought through several carbon-carbon bond-forming reactions, protections and deprotections, and then finally unveiled using a singlet oxygen cleavage.[4] A number of earlier natural products syntheses using a similar overall strategy are described in the Wasserman review.[2] For the oxidative cleavage of 2,4,5-trisubstituted oxazoles in general, a number of options are available and may be applied to diverse substrates depending on the presence of other functional groups.[5] A product which is common to most 2-substituted-4,5-diphenyloxazole oxidative cleavage reactions is the triacylamine whereby two of the acyl groups are benzoyl.[6] The remaining acyl group is derived from the 2-oxazole substituent and is incorporated in the target molecule where it can ultimately be transformed to a carboxylic acid, amide, ester or lactone. Our recent work with the preparation and utilization of 4,5-diphenyl-2-extended oxazoles as fundamental synthetic scaffolds has prompted us to examine and expand the available options for the conversion of the 2-substituted-4,5-diphenyloxazole group to the 'corresponding' carboxylic acid derivative(s) (**Scheme 1**).[7] We demonstrate



Scheme 1. General 2-substituted-4,5-diphenyloxazole cleavage and further transformations.

herein a new method for oxidative cleavage of the title trisubstituted oxazoles using a readily-available reagent system composed of a peroxide (*m*-chloroperbenzoic acid, MCPBA), and an oxochromium (VI) reagent (2,2-bipyridinium chlorochromate, BPCC).[8] The two-component reagent system is operationally simple and utilizes components which are readily-available and inexpensive. While taken individually or together,

the oxochromium (VI) and peroxide reagents represent rather robust reactants, the reagent system appears to be compatible

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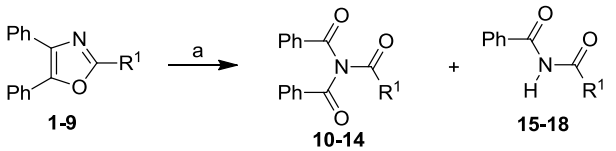
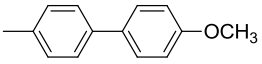
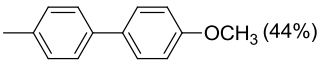
Table 1
Oxidative cleavage reactions of trisubstituted oxazole substrates **1-9**.



1-9 **10-14** **15-18**

Substrate	Triacylamine (%)	Diacylamine (%)
1, R^1=Ph	**10**, R^1=Ph (71%)	
2, R^1=4-BrC_6H_4	**11**, R^1=4-BrC_6H_4 (66%)	
3, R^1=4-IC_6H_4	**12**, R^1=4-IC_6H_4 (64%)	
4, R^1=4-$CH_3OC_6H_4$	**13**, R^1=4-$CH_3OC_6H_4$ (62%)	
5, R^1= 	**14**, R^1=  (44%)	
6, R^1=*n*-C_5H_{11}		**15**, R^1=*n*-C_5H_{11} (38%)
7, R^1=*n*-C_7H_{15}		**16**, R^1=*n*-C_7H_{15} (41%)
8. R^1=cyclopentyl		**17**, R^1=cyclopentyl (60%)
9, R^1=cyclohexyl		**18**, R^1=cyclohexyl (55%)

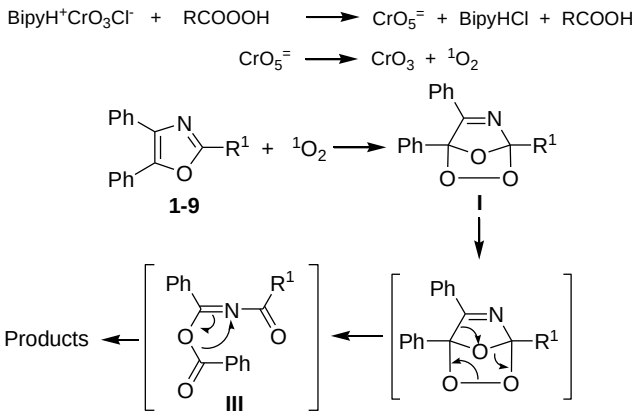
Reagents/Conditions: (a) MCPBA(5eq)/BPCC (2eq)/0-20 ^oC/2-3 h.

with a range of oxazole substrates. The reactions are fairly rapid and provide the pure triacylamines or diacylamines (imides) after column chromatography on silica gel. We should note that while singlet oxygen has been the reagent of choice for the oxazole→triamide transformation, the employment of a ceric ammonium nitrate/water (CAN/H_2O) reagent system was also disclosed by the Evans group as an alternative method albeit a viable one in total synthesis.[5b] By comparison, we feel that the BPCC/MCPBA is an additional alternative to the singlet oxygen or CAN-mediated methods.

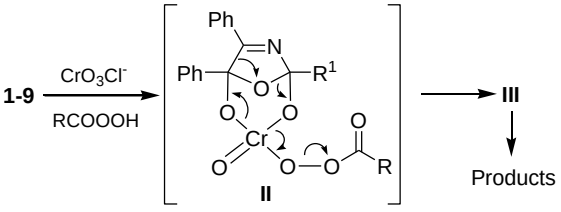
The reaction conditions employed for the oxidative cleavage were established using the benchmark substrate 2,4,5-triphenyloxazole **1** (**Table 1**).[9] In a typical procedure, two equivalents of BPCC and five equivalents of MCPBA in dichloromethane were used, and as the reaction proceeds, the less chromatographically-mobile triacylamine **10** could be detected by thin-layer chromatography (TLC). The reaction mixtures were yellow-orange heterogeneous suspensions with BPCC being the only partially insoluble component. Application of the same conditions to a number of 2-substituted-4,5-diphenyloxazole substrates **2-9**, differing only in substitution at the 2-position of the oxazole, gave the products **10-18** as listed in **Table 1**. Interestingly, the diacylamine (imide) products **15-18** were formed during the reaction of the 2-alkyl-4,5-diphenyloxazole substrates **6-9**, while the triacylamine products **10-14** were formed from the 2-(aryl-substituted) substrates **1-5** respectively. Control reactions which utilized the same solvent and either the peroxyacid or the chromium reagent alone did not facilitate the cleavage. Moreover, the substitution of the less expensive and more shelf-stable pyridinium chlorochromate (PCC) for BPCC, using the same ratio of reagents, resulted in vigorous decomposition of the peroxide and did not provide the title products. The best results were obtained with freshly-prepared, dried BPCC or reagent which was not more than a few weeks old, stored under nitrogen and protected from light. We will note that in contrast to some previously-reported BPCC/peroxide-mediated oxidations,[10] which utilized only a catalytic amount of oxochromium reagent, a full two equivalents is required in the reaction reported herein.

In terms of general mechanism, the generation of peroxychromium (VI) species from peroxides and oxochromium (VI) has been reported (**Scheme 2**, Path A).[11] The reactions occur

Path A. Singlet oxygen/endoperoxide pathway:



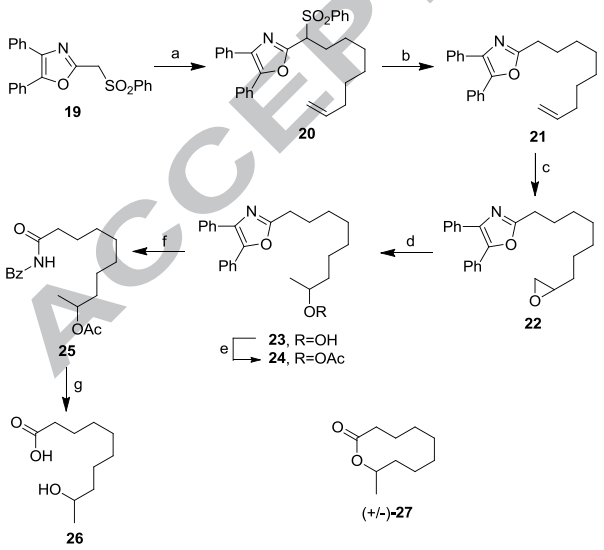
Path B. Oxachromacycle pathway:



Scheme 2. Mechanistic pathways of trisubstituted oxazole cleavage.

under homogeneous conditions in organic solvents, and the generation of the highly-reactive peroxychromate species is characterized by an intense transient deep-blue color. In turn, thermal decomposition of the short-lived peroxychromium species is known to generate singlet oxygen which is an established reactant in trisubstituted oxazole cleavage and results in intermediate endoperoxide **I**.[5a] Through multiple pathways, including rearrangement of **I** and acyl migration through the acyliminoester **III**, the oxidative cleavage then results in the formation of the tri- and diacylamine products **10-18**.[5a] As the reaction conditions are heterogeneous and exhibit the yellow-orange color due to BPCC, it is difficult to detect the characteristic deep-blue color of peroxychromate and confirm Path A.[12] A second mechanistic consideration (**Scheme 2**, Path B) involves delivery of oxygen to the heterocycle via the intermediate oxachromacycle **II**.[13a] Similar intermediates have been proposed in the oxidative cleavage of 2,5-disubstituted furans to enediones by oxochromium (VI) as exemplified by BPCC and PCC.[13b, 14] Rearrangement of **II**, then gives reduced chromium species, *m*-chlorobenzoic acid and the common intermediate **III**, which in turn, rearranges to products **10-18**.

We demonstrate the practical utility of our oxidative cleavage reaction by the synthesis of (±)-phoracantholide I *seco*-acid **26**, the acyclic precursor to the macrocyclic lactone, phoracantholide I (**27, Scheme 3)** which is a naturally-occuring component of insect pheromones.[15] The synthesis of **26** starts with the key 2-(phenylsulfonylmethyl)-4,5-diphenyloxazole **19** (**Scheme 3**). The diphenylsulfonylmethyloxazole **19** is alkylated with 8-bromo-1-octene in the presence of potassium *tert*-butoxide (THF/5 ºC to rt) which affords the 2-nonenyl-2-(phenylsulfonyl methyl)-4,5-diphenyl-oxazole **20** in 66% yield. The phenylsulfonyl group of **20** was then removed under reductive conditions ($Mg/HgCl_2$/MeOH) to give the 2-nonenyloxazole **21** (79%). Epoxidation of the olefinic oxazole **21** using 30% hydrogen peroxide in the presence of DCC ($KHCO_3$/MeOH) provided the epoxynonanyloxazole **22** (85%). Interestingly, during the conversion of **21**→**22** the 4,5-diphenyloxazole moiety was not affected by the peroxide, even after extended reaction periods.



Scheme 3. Synthesis of (+/-)-phoracantholide I *seco*-acid **26**. Reagents/Conditions: (a) KOt-Bu/8-bromo-1-octene/THF/5 ºC to rt/16 h (66%); (b) $Mg/HgCl_2$/MeOH/rt/ 16 h (79%); (c) H_2O_2/DCC/$KHCO_3$/MeOH/rt/16 h (85%); (d) $LiAlH_4$/THF/0ºto 10ºC/3 h (80%); (e) Ac_2O/TEA/DMAP/CH_2Cl_2/reflux/2 h (72%); (f) MCPBA/BPCC/ CH_2Cl_2/5-20ºC/3 h (40%); NaOH/MeOH then conc HCl/pH=2 (88%).

Exposure of the epoxynonyloxazole **22** to excess lithium aluminum hydride in THF (0→10 ºC) afforded the oxazolynonyl secondary alcohol **23** (80%) which was first characterized as the corresponding acetate **24** (acetic anhydride/triethylamine/DMAP, 72%). The oxazole-alcohol **23** was submitted to the oxidative cleavage reaction with the hopes that the expected amide or imide cleavage products would lactonize directly to **27**. However, the oxidation of the secondary alcohol **23** to the corresponding methyl ketone **28** predominated over a lengthy (16 h) reaction period. Treatment of oxazoleacetate **24** with MCPBA/BPCC (2eq/5eq, 5 ºC→20 ºC, CH_2Cl_2) gave acetoxyimide **25** (40%). Finally, hydrolysis of the acetoxyimide **25** (NaOH/MeOH) and adjustment of the reaction mixture to pH=2 provided the (±)-*seco* acid **26** (88%).

In summary, we have detailed a new method for the oxidative cleavage of 2-substituted-4,5-diphenyl oxazoles to triacylamines and diacylamines. The method is a complementary or otherwise alternative one to the well-established method of photolysis/singlet oxygen and utilizes readily-available reagents. The substrates having alkyl groups at the 2-position give the imide products while substrates having aryl groups at the 2-position give the triacylamines. Using the 4,5-diphenyl-2-(phenylsulfonylmethyl) oxazole group as a synthon, the oxazole served as a masked carboxylic acid equivalent in our synthesis of phoracantholide I seco acid. Ultimately, the oxidative cleavage was a key step in the *seco* acid synthesis, but the stability of the 4,5-diphenyloxazole group to reagents such as magnesium/$HgCl_2$, hydrogen peroxide and lithium aluminum hydride was also demonstrated.

Acknowledgments

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Supplementary Material

General procedures and supplementary data (FTIR, ^{1}H NMR, ^{13}C NMR) for compounds **5**, **10-18**, **20-16** and HRMS data for new compounds **5**, **12**, **14**, **20-25** associated with this article can be found, in the online version, at http://dx.doi.org/ 00.1017/j.tetlet.

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Highlights

- **A new method for the oxidative cleavage of 2,4,5-trisubstituted oxazoles to imides and triacylamines is detailed.**
- **The oxidation system utilizes a dual reagent system composed of a peroxide and oxochromium (VI).**
- **Mechanisms are proposed for the oxidative cleavage reaction.**
- **A synthesis of (±)-phoracantholide *seco*-acid is detailed which utilizes the oxidative cleavage reaction to ultimately give a carboxyl function through the product imide.**