Tetrahedron Letters, Vol. 33, No. 47, pp. 7207-7210, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

SINGLET OXYGEN IN SYNTHESIS. OXAZOLES AS CARBONYL 1,1-DIPOLE SYNTHONS.

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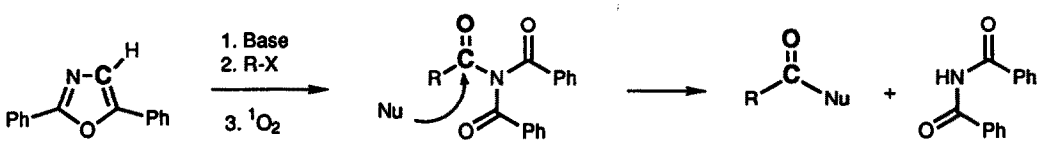
Abstract: *2,5-Diphenyloxazole has been utilized in a two-step sequence as a carbonyl 1,1-dipole synthon as illustrated by the synthesis of 7-heptanolide, α-benzyloxy δ-valerolactone, and 9-nonanolide. Alkylation of 4-lithio-2,5-diphenyloxazole, followed by singlet oxygen oxidation yields a triamide which undergoes cyclization to the lactone.*

In earlier studies,[1] we have shown that oxazoles undergo ready oxidative rearrangement to triamides by the action of singlet oxygen. Through this facile conversion, each of the carbon atoms of the heterocyclic ring functions as a latent activated carboxyl equivalent, permitting use of the oxazole molecule as a carboxylic acid protecting group. We have also shown that a methylene group at the 2-position of 4,5-diphenyloxazole may be substituted *via* metallation for reaction with electrophiles. In this sense, the ring 2-carbon atom and the adjacent methylene group function as an activated acetic acid anion equivalent.[2] In more recent work, 2,5-diphenyl-4-chloromethyloxazole has been employed as an activated acetic acid cation equivalent in the synthesis of (±)-pyrenolide C.[3]

We now report a novel two-step sequence for generating a carbonyl 1,1-dipole synthon from an oxazole precursor.[4] The first step involves direct substitution of a hydrogen at the 4-position of the oxazole ring *via* metallation, followed by reaction with an alkyl halide or a carbonyl derivative. Subsequent oxidation with singlet oxygen converts the heterocyclic system to a triamide, ready for reaction with a nucleophilic species. If the nucleophile undergoes selective acyl attack (with the R-C=O) the latent carbonyl at the 4-position of the oxazole will have reacted sequentially as an anionic site, and then, after photooxidation, as a cationic center. The general procedure is outlined below (Scheme 1).



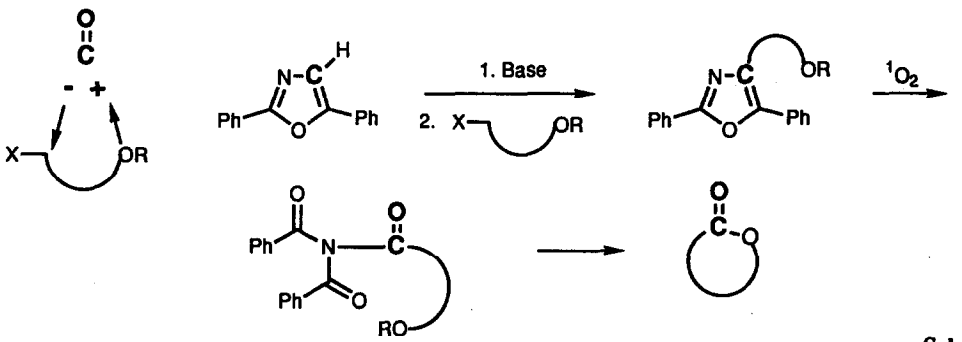
Scheme 1

Our early experiments were carried out with 4,5-diphenyloxazole, which could be metallated at the 2-position using various bases, however, undesirable ring opening processes accompanied these reactions. Initially, *n*-butyllithium was used to generate the 4-lithiated 2,5-diphenyloxazole, but this reagent led to

substantial butyl substitution at the 2-position. On the other hand, lithium diisopropylamide was effective in deprotonating the 4-position at -78°C with no undesirable substitution.

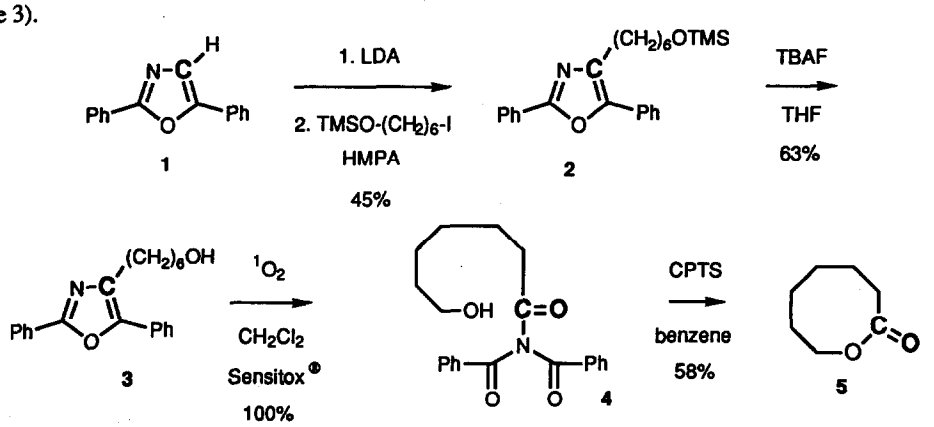
Once generated, the 4-lithio oxazole showed the expected reactions with electrophiles, such as aldehydes, ketones and primary alkyl halides. Acid chlorides reacted with 2 equivalents of the oxazole anion to form tertiary alcohols, while esters, imines and epoxides appeared to be unreactive with or without added $BF_3{\cdot}Et_2O$. In all cases studied, photooxidation of the trisubstituted oxazoles proceeded smoothly to afford the corresponding triamides in nearly quantitative yield.

The second stage of this sequence involved reaction of the intermediate triamide with nucleophiles (Scheme 1). While these carbonyl addition reactions showed a lack of regioselectivity in intermolecular reactions,[5] the intramolecular counterparts showed a remarkable preference for acyl versus aroyl attack. In the present work, we have taken advantage of this selectivity in synthesis of lactones, as outlined in Scheme 2.



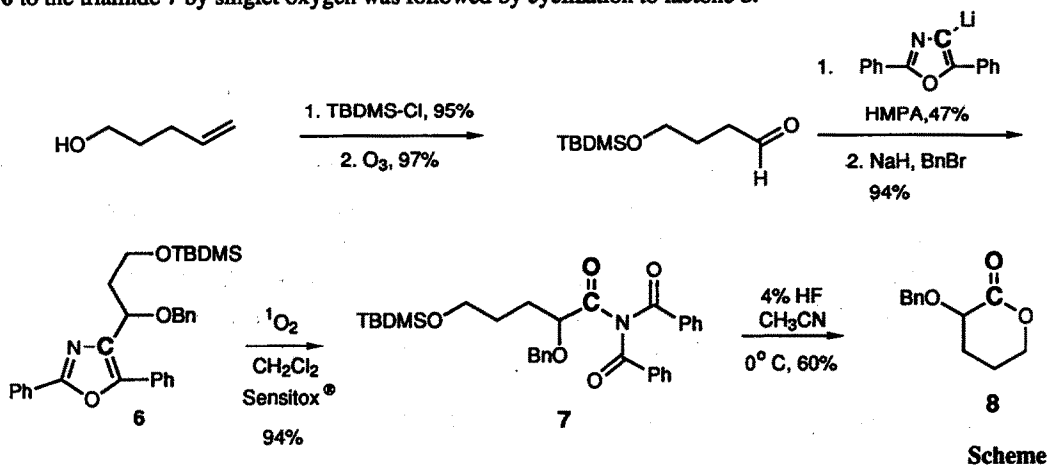
Scheme 2

The 4-lithio derivative of 2,5-diphenyloxazole was formed by treating **1** with LDA in anhydrous THF at -78°C. The resulting solution was then stirred with the TMS derivative of 6-iodohexanol, followed by addition of HMPA (2 equiv.). The product **2** was desilylated with TBAF in THF, and the alcohol **3** subjected to dye-sensitized photooxygenation in CH_2Cl_2 (Sensitox®). The triamide **4** which resulted in quantitative yield was then cyclized in dilute benzene in the presence of collidine *p*-toluene sulfonate to form 7-heptanolide **5** (58%) (Scheme 3).



Scheme 3

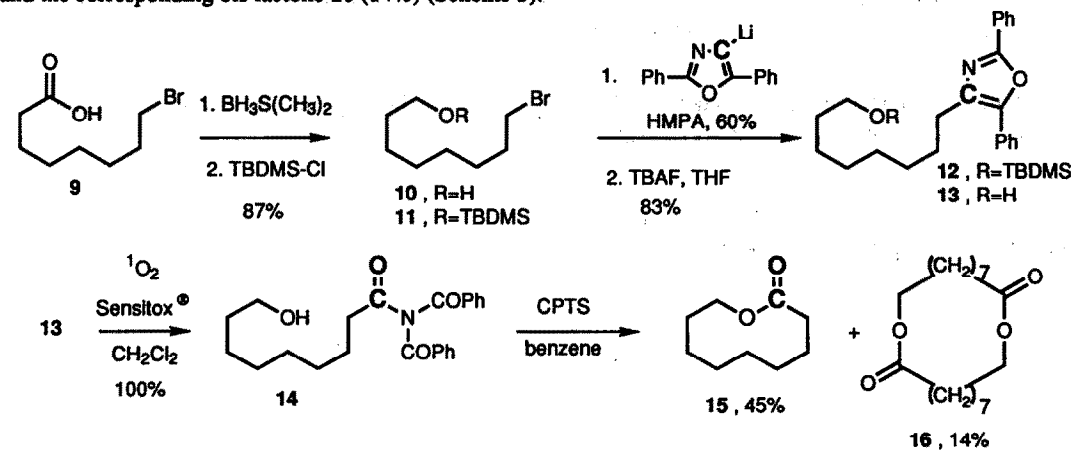
Use of an aldehyde as the electrophilic component in the reaction with the 4-lithio derivative of **1** is illustrated in the synthesis of the α-benzyloxy δ-valerolactone (**8**). In this case, the carbonyl dipole unit provided by 2,5-diphenyloxazole (**1**) was inserted between the donor and acceptor components of 4-hydroxybutanal. The reaction sequence leading to the oxazole precursor **6**, is shown in Scheme 4. Conversion of **6** to the triamide **7** by singlet oxygen was followed by cyclization to lactone **8**.



Scheme 4

In another macrolide synthesis (Scheme 5), 8-bromooctanoic acid (**9**) was reduced quantitatively to 8-bromoctanol (**10**) with borane dimethylsulfide complex.[6] The alcohol was protected as the *t*-butyldimethylsilyl derivative **11** by reaction with TBDMS-Cl (87%). Addition of a solution of the silyloxybromide **11** and HMPA to the lithio oxazole furnished the alkylated product **12** (60%).[7]

Desilylation of **12** with TBAF provided the desired hydroxyoxazole **13** (83%) which was then reacted with singlet oxygen forming the the corresponding triamide **14** in quantitative yield. A benzene solution of **14** was then added slowly (*ca.* 60 h *via* syringe pump) to a refluxing solution of collidinium *p*-toluene sulfonate (CPTS) in benzene under high dilution. Purification of the crude product on silica gel afforded 9-nonanolide (**15**) (45%) and the corresponding bis lactone **16** (14%) (Scheme 5).



Scheme 5

We are exploring other applications of this reaction sequence in which 2,5-disubstituted oxazoles serve as 1,1-carbonyl dipole equivalents.

Acknowledgements: Support for this research was provided by Grant 13854 from the General Medical Sciences Institute of the National Institute of Health.

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3. Wasserman, H.H.; Prowse, K.S. *Tetrahedron Lett.* **1992**, *33*, 5423.

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5. Clear preference for acyl versus aroyl attack was shown in the reactions of triamides with amines forming di- and tripeptides. Wasserman, H.H.; Lu, T.-J. *Tetrahedron Lett.* **1982**, *23*, 3831.

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7. A dehydrohalogenated side-product was also isolated (10%), indicating that elimination competes to a small extent with alkylation of the C-4 anion.

(Received in UK 11 September 1992)