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ACTIVATED CARBOXYLATES FROM THE PHOTOOXYGENATION OF OXAZOLES. APPLICATION TO THE SYNTHESIS OF RECIFEIOLIDE AND OTHER MACROCYCLIC LACTONES.

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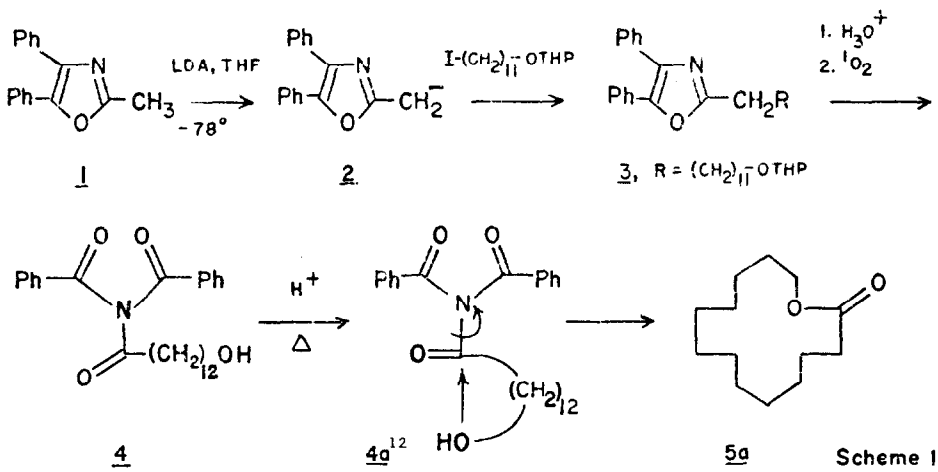
SUMMARY: The oxazole system may serve as a protecting group for the carboxyl function. The carboxylate is generated under the mild conditions of photooxygenation in high yield in the form of the reactive triamide. This reaction has been applied to the synthesis of macrocyclic lactones.

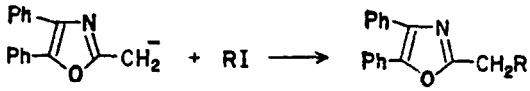
The conversion of oxazoles to triamides by dye-sensitized photooxidation is of special interest among the reactions of singlet oxygen with heterocyclic systems.[1,2] This remarkable rearrangement, taking place in high yields under mild conditions, effectively transforms each of the oxazole ring carbon atoms to a carboxylate derivative. Using 2-alkyl-4,5-diaryloxazoles as substrates, this photooxidation procedure may be employed to unmask a powerful latent acylating agent, since the acyl carboxyl group formed at the 2-position, the sterically favored site for nucleophilic attack, is generated in a highly activated (triamide) form. We have now shown that the oxazole-triamide rearrangement may be utilized in a general synthesis of lactones ranging from five and six-membered units to macrocyclic systems.[3]



Scheme I

In our work we have used the readily available 2-methyl-4,5-diphenyloxazole (1)[4] to provide the building unit containing the protected carboxylate. Alkylation of the 2-methyl group was accomplished using LDA at -78°C in THF to generate the anion (2) which could then be reacted with the required electrophile to form 3 as summarized in Table I.[5,6] In our initial studies on this reaction, the anion (2) was treated with propylene oxide to form the alcohol (3, R = $CH_2CH(CH_3)OH$) (45%) which, on reaction with singlet oxygen, was converted directly to 4-methylbutyrolactone (50%) without isolation of the intermediate triamide. In subsequent work, we have chosen conditions which favor the isolation of the triamide. Intramolecular acylation of the ω-hydroxyl group then takes place under acid catalysis and dilution.

Table I.



2 3

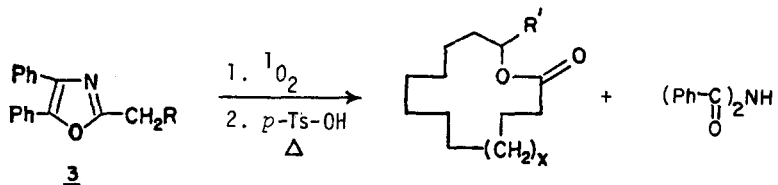
entry	RI	Yield, %
(1)	CH_3I	73
(2)	$CH_3CH_2CH_2$-I	82
(3)	THPO-$(CH_2)_{11}$-I	57*
(4)	THPO-$(CH_2)_{12}$-I	43*
(5)	THPO-CH(CH_3)-$(CH_2)_{11}$-I	40*
(6)	THPO-CH(CH_3)-CH_2-CH=CH-$(CH_2)_5$-I	43*

**Yield of alcohol after hydrolysis of THP ethers*

For preparation of the large ring lactones (5a, 5b, 5c, 6) (Table II) alkylation of the anion (2) with the appropriate ω-iodo-(O-tetrahydropyranyl)alkanol was followed by acid promoted deprotection of the alcohol. In the case of recifeiolide (6)[7,8] our synthesis employed the THP ether of 5-tributylstannyl-4-penten-2-ol reported by Corey.[8] The mixture of E- and Z-isomers (85:15) obtained in this sequence was converted to the corresponding cuprates by treatment with n-butyllithium and pentynylcopper as reported.[8] This product was then treated with 1-chloro-5-iodopentane and then sodium iodide in acetone to form the iodo THP ether (entry 6, Table I). Reaction of this mixture with anion (2) followed by acid hydrolysis yielded 3. Photooxidation and cyclization as shown in Table II gave a mixture of E- and Z-(±)recifeiolide from which the pure E-form could be isolated by chromatography on silver nitrate-impregnated silica gel. The synthetic material was identical with natural recifeiolide (NMR, IR, TLC).[9]

The formation of 13-tridecanolide (5a) is outlined as a typical procedure (Scheme I). To a solution of LDA in 15 mL of THF (2.4 mmol) at -78°C was added 0.564 g (2.4 mmol) of 2-methyl-4,5-diphenyloxazole in 10 mL of THF over 30 min. The carmine-red mixture was stirred for an additional h, then treated at -78°C with 0.917 g of 11-iodo-(O-tetrahydropyranyl)undecanol. After 10 min, the mixture was quenched with water and the solvent removed under reduced pressure. The solid was taken up in ether, washed with water, dried, and the solvent removed. The residue was diluted with THF (50 mL) containing 2N HCl, and heated at 60°C for 3 h. Removal of solvent and flash chromatography on silica gel (1:1 ether:hexane) yielded 0.554 g (57%) of hydroxyoxazole (3, R=$(CH_2)_{11}$-OH) mp 65-67°C (ether-hexane); NMR ($CDCl_3$, 90 MHz) δ 1.2-1.7 (m, 20H), 2.82 (t, J = 7.5 Hz, 2H), 3.54 (t,J = 6.0 Hz, 2H), 7.2-7.4 (m, 6H) and 7.5-7.7 (m, 4H); IR 3600 cm^{-1}.

Table II.



3

R	Lactone	Yield,%
$(CH_2)_{11}$-OH	5a; x=2, R'=H	75
$(CH_2)_{12}$-OH	5b; x=3, R'=H	76
$(CH_2)_{11}$-CH(CH3)-OH	5c; x=2, R'=CH_3	64
$(CH_2)_5CH{=}CHCH_2CH(CH_3)$-OH	6	55*

mixture of E- and Z-isomers

Macrolide formation proceeded in the following manner: A solution of the hydroxyoxazole (3, R=$(CH_2)_{11}$-OH) (0.405 g, 1 mmol) in 100 mL of CH_2Cl_2 was oxygenated in the presence of Sensitox (Rose Bengal polymer) (40 mg) during irradiation with a tungsten-halogen light source (650 w) for 30 min. After removal of Sensitox by filtration and evaporation of the solvent, an oil (4) was obtained, to which was added 35 mL of benzene, and the solution injected (during 24 h) into refluxing benzene (100 mL) containing a trace of p-toluenesulfonic acid. The mixture was cooled, washed with satd. $NaHCO_3$, dried, and the solvent removed leaving an oily residue which was taken up in ether and thus separated from the insoluble coproduct, benzoylbenzamide. Chromatography on silica gel gave pure 13-tridecanolide (5a) (0.160 g, 75%) which was identical in all respects with an authentic sample.[10]

The above examples show that the oxazole system, which is relatively stable to acids and bases, may serve as a protecting group for the carboxyl function. We are currently studying further uses of oxazoles as protecting groups for carboxylates in the synthesis of lactones and lactams.

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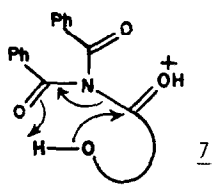
REFERENCES AND FOOTNOTES

1. H.H. Wasserman and M.B. Floyd, Tetrahedron, Suppl. 7, 441 (1966); H.H. Wasserman, F.J. Vinick and Y.C. Chang, J. Am. Chem. Soc., 94, 7180 (1972).
2. For a recent review, see: H.H. Wasserman and B.H. Lipshutz, in "Singlet Oxygen", H.H. Wasserman and R.W. Murray, Eds., Academic Press, New York, 1979, Chapter 9.
3. K.C. Nicolaou, Tetrahedron, 33, 683 (1977); S. Masamune, G.S. Bates and J.W. Corcoran, Angew. Chem. Int. Ed. Engl., 16, 585 (1977); T.G. Back, Tetrahedron, 33, 3041 (1977).
4. D. Davidson, M. Weiss and M. Jelling, J. Org. Chem., 2, 328 (1937).
5. For an early report on the alkylation of 2-methyl-4,5-diphenyloxazole see V. Dryanska and Khr. Ivanov, God. Sofii. Univ. Khim. Fak., 63, 105 (1971); Chem. Abstr., 76, 126844 (1972).
6. For recent studies on the metalation and alkylation of trisubstituted oxazoles see B.L. Lipshutz and R.W. Hungate, J. Org. Chem., in press.
7. Isolation of recifeiolide: R.F. Vesonder, F.H. Stodola, L.J. Wickerham, J.J. Ellis and W.K. Rohwedder, Can. J. Chem., 49, 2029 (1971); R.F. Vesonder, F.H. Stodola and R.W. Rohwedder, Can. J. Biochem., 50, 363 (1972).
8. For previous syntheses of recifeiolide see: E.J. Corey, P. Ulrich and J.M. Fitzpatrick, J. Am. Chem. Soc., 98, 222 (1976); H. Gerlach, K. Oertle and A. Thalmann, Helv. Chim. Acta, 59, 755 (1976); K. Narasaka, M. Yamaguchi and T. Mukaiyama, Chem. Lett., 959 (1977); K. Utimoto, K. Uchida, M. Yamaya and H. Nozaki, Tetrahedron Lett., 3641 (1977); T. Takahashi, S. Hashiguchi, K. Kasuga and J. Tsuji, J. Am. Chem. Soc., 100, 7424 (1978); J. Tsuji, T. Yamakawa and T. Mandai, Tetrahedron Lett., 565 (1978); B.M. Trost and T.R. Verhoeven, J. Am. Chem. Soc., 102, 4743 (1980); S.L. Schreiber, J. Am. Chem. Soc., 102, 6163 (1980).
9. We are grateful to Dr. R.F. Vesonder, U.S. Dept. of Agriculture, Peoria, Ill., for an authentic sample of 11-hydroxy-trans-8-dodecenoic acid lactone (recifeiolide). We also thank Dr. R. Kaiser, Givaudan, Forschungsgesellschaft AG, Zurich, for reference samples of 14-tetradecanolide (5b) and 14-pentadecanolide (5c).
10. Lactone (5a) was compared with an authentic sample prepared by the Baeyer-Villiger ring expansion of cyclotridecanone: L. Ruzicka and M. Stoll, Helv. Chim. Acta, 11, 1159-73 (1928).
11. Satisfactory spectroscopic data ['H NMR, IR] were obtained for all compounds. All of the lactones prepared in this work were compared with authentic samples (see references 9 and 10).
12. Macrolide formation is shown schematically in 4a. We are investigating the possibility that, under acid catalysis, the intramolecular cyclization may take place through an intermediate such as 7.



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