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Di-tert-Butyl Pyrocarbonate Mediated Synthesis of Macrocyclic Lactones From ω-Hydroxy Acids

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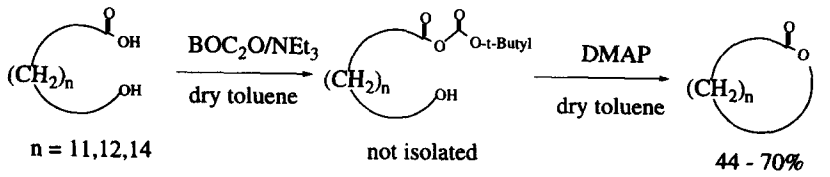
Abstract: A new and facile method for the synthesis of macrocyclic lactones was achieved from ω-hydroxy acids using Di-tert-butyl pyrocarbonate [BOC_2O], a cheap and commercially available reagent.

Di-tert-butyl pyrocarbonate [BOC_2O] is a widely used reagent for the introduction of the BOC-protecting group in amino acids, peptides and proteins.[1] This is an efficient t-butoxycarbonylating agent for alcohols, thiols, amines and various carbon nucleophiles.[2] It has also been used in the synthesis of isocyanates from primary amines.[3,4] Recently this reagent has been used for the synthesis of esters from carboxylic acids by V.F. Pozdnev[5] and Takeda et al.[6] During the course of the synthesis of azamacrolides,[7] a new class of defensive compounds, we have discovered that BOC_2O can be used as an efficient reagent for the activation of carboxylic acids for the synthesis of macrocyclic lactones. Based on the Pozdnev method we have developed the BOC_2O mediated macrolactonisation of ω-hydroxy acids.

Macrocyclic lactones constitute an important class of natural products possessing diverse biological activities, like antibiotic, antitumour etc. As a result, a variety of approaches[8] have been developed for their synthesis. The macrolactonisation is generally involved in the final stages during the synthesis of macrolides. Therefore the reagents and reaction conditions employed should be mild and efficient, so as not to affect the other sensitive functionalities that might be present in the molecule. The widely used approach for the synthesis



Scheme-1

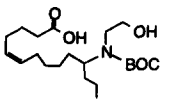
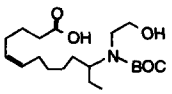
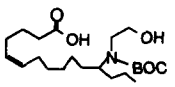
of these lactones is by ring closure of the corresponding ω-hydroxy acids, which involves the activation of the carboxylic acid followed by nucleophilic displacement of the leaving group by the hydroxy moiety in an intramolecular fashion.

Our method mainly involves two steps (i) the activation of the carboxylic acid by converting it into its mixed anhydride (ii) macrolactonisation of the resultant mixed anhydride under high dilution conditions (Scheme-1). Of various solvents screened (acetonitrile, benzene, dioxane, dichloromethane, toluene), good yields of lactones were obtained in toluene. The following series of lactones was prepared from the corresponding ω-hydroxy acids using this BOC_2O technique (Table 1).

In the first step, the hydroxy acid was treated with BOC_2O to get the mixed anhydride in the presence of triethylamine, which on slow addition to 8 equivalents of DMAP in dry toluene under high dilution conditions gave the lactone. Triethylamine was found to give better yields of lactones, whereas in the case of pyridine, we observed low yields of lactone formation (Table 1, Entry 4).

Table - 1

Lactonization of ω-hydroxy acids:

S.No	ω-hydroxy acid	Ring size	Base	yield %[a] lactone	Diolide
1.	$HO-(CH_2)_{11}-COOH$	13	NEt_3	44	27
2.	$HO-(CH_2)_{12}-COOH$	14	NEt_3	64	24
3.	$HO-(CH_2)_{14}-COOH$	16	NEt_3	71	20
4.	$HO-(CH_2)_{14}-COOH$	16	Pyridine	34	19
5.		15	NEt_3	53	-
6.		15	NEt_3	55	-
7.		16	NEt_3	54	-

a - Isolated yield

General procedure:. A mixture of ω-hydroxy acid (0.4 mmol) and triethylamine (1.6 mmol) in dry-toluene (3 ml) was stirred for 10 min. at room temperature under N_2 and then di-tert-butyldicarbonate (BOC_2O) (1.6 mmol) was added. After stirring for 2 h at room temperature, the reaction mixture was diluted with dry toluene (210 ml) and slowly added to a hot solution (90°C) of 4-dimethylaminopyridine (3.2 mmol) in dry toluene (50 ml) over a period of 4-5 h. The reaction was continued for 12 - 15 h at 90 - 95°C. Then the reaction mixture was concentrated and diluted with diethyl ether, washed successively with aqueous citric acid, water and brine solution. The organic portion was dried and concentrated followed by column chromatography to give the lactone.

In entries **1** to **4**, the lactones were characterised by ^1H NMR, MS, HRMS or microanalysis, and the spectral data were also in agreement with the reported values.[8] Entries **5, 6, 7** are key intermediates for the synthesis of the azamacrolides [Epilachnene (I), Norepilachnene (II) and Homoepilachnene (III)].[7,9] The lactones resulting from these sequences were subjected to trifluoroacetic acid treatment to give azamacrolides I, II, III respectively,[9] whose spectral data were in accordance with the compounds synthesized[7] by the Yamaguchi macrolactonisation technique.[10]

In conclusion, we have developed a mild and novel process for making lactones using the commercially available BOC_2O reagent in good yields. The above method also involves simple work up procedure. Improvement of the reaction conditions, yields and application of this methodology to the synthesis of complex natural products are in progress.

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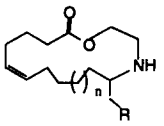
9. 

Epilachnene - I n = 1, R = Et
Norepilachnene - II n = 1, R = Me
Homoepilachnene - III n = 2, R = Et

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