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Cleavage of Chiral 4-Phenyl-2-Oxazolidinones with TMSI: Application to the Synthesis of Carbacephems

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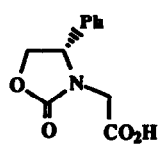
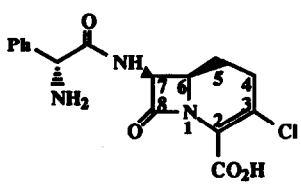
Abstract: *A new technique for cleaving chiral N-substituted 4-phenyl-2-oxazolidinones is described. Thus reaction of a 7-[4-phenyl-2-oxazolidinone]-carbacephem with TMSI and HMDS in acetonitrile, followed by DABCO, then aqueous hydrochloric acid gives the carbacephem nucleus, carbon dioxide, and acetophenone. This method allows a more versatile use of 4-phenyl-2-oxazolidinone as a chiral auxiliary and N-protective group in the synthesis of carbacephems.*

The first enantioselective synthesis of carbacephems[1] employed a [2 + 2] cycloaddition reaction using the S-4-phenyl-2-oxazolidinone chiral auxiliary **1**. This chemistry was later utilized in the synthesis[2] of loracarbef **2**, the first antibiotic of the carbacephem class of ß-lactams to undergo clinical development. Further improvements in the strategy for synthesis of this class of compounds were realized when the Dieckmann cyclization became the method of choice for forming the key six-membered ring[3]. Since only the glycine portion is utilized as a part of the final product, simple techniques for removing the chiral auxiliary were essential. A Birch reduction proved to be most efficient[1] and remains the method of choice. However the instability of 3-substituted carbacephems to conditions of the Birch reduction necessitated early removal of the 4-phenyl-2-oxazolidinone and replacement with other nitrogen protective groups, thus adding steps to an already lengthy synthesis. We describe herein a simple method for cleaving 4-phenyl-2-oxazolidinones, which can be applied to sensitive ß-lactams, and which substantially reduces the requirements for additional nitrogen and carboxyl blocking groups in the synthesis of carbacephems.



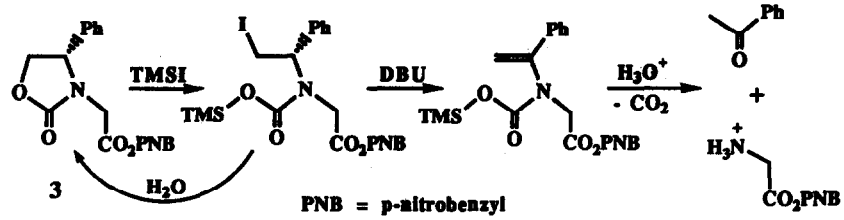
1



2

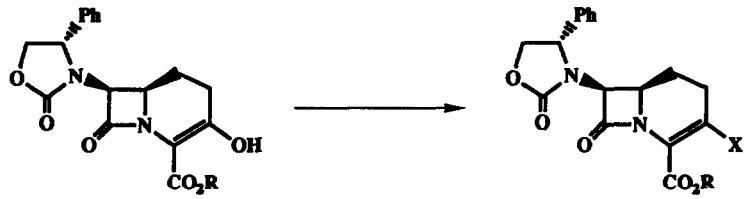
Initially, we explored the oxazolidinone ring opening with the simple derivative **3**, prepared from **1** by esterification with p-nitrobenzyl bromide and triethylamine in DMF at room temperature. Treatment of **3** with

trimethylsilyl iodide[4] in methylene chloride at room temperature followed by addition of DBU to effect elimination of HI, then hydrolysis of the enamine in acetonitrile with aqueous 1N hydrochloric acid[5] gave the hydrochloride salt of glycine p-nitrobenzyl ester and acetophenone (Equation 1). Gas evolution (carbon dioxide) occurred during the hydrolysis stage and the characteristic odor of acetophenone was clearly present. Both acetophenone and the p-nitrobenzyl ester of glycine were isolated and fully characterized.



Equation 1

In order to test this reaction on a more complex substrate, the ß-lactam enol **4** was prepared from S-4-phenyl-2-oxazolidinone **1** according to literature procedures[1,2,3b]. Enol chlorination with triphenyl phosphite dichloride[6] gave the 3-chlorocarbacephem **5**. The 3-trifluoromethyl compound **6** was prepared by first converting **4** to the enol triflate **7** with triflic anhydride, followed by bromide displacement using lithium bromide and Hunig's base in DMF at room temperature, and then reaction with trifluoromethyl copper reagent in DMF[7] (Equation 2).



4a R = Me
4b R = PNB

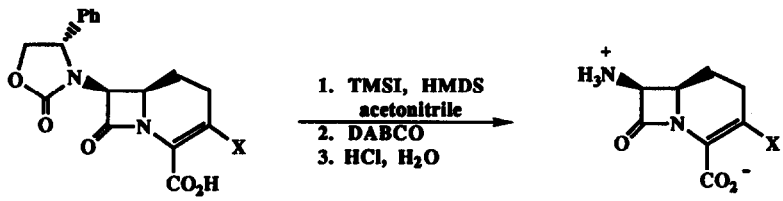
5a X = Cl R = Me
5b X = Cl R = PNB
6 X = CF_3
7 X = OTf
8 X = Br
9 X = I

Equation 2

With these compounds it was anticipated that both the oxazolidinone and the carboxylic ester group would be cleaved with TMSI[8]. Indeed, treatment of **5 a** (R = Me) with trimethylsilyl iodide and hexamethyldisilazane (HMDS) in acetonitrile at reflux, followed by DABCO[9] at room temperature, then careful neutralization with aqueous hydrochloric acid resulted in the direct crystallization (71% yield) of the nucleus **15**, identical in all respects to that previously reported[10]. The ß-lactams required the addition of a weak base such as hexamethyldisilazane or pyrimidine to moderate the acidity of the reaction mixture in order

to avoid HI catalyzed decomposition. Reaction of the PNB ester (**5b**) with TMSI resulted in significant degradation and in practice it proved more efficient to remove the PNB ester with zinc and hydrochloric acid prior to cleavage of the oxazolidinone with TMSI.

Carbacephem carboxylic acids containing the oxazolidinone were rapidly silylated in acetonitrile at room temperature by addition of 2.5 eq. HMDS followed by 2.5 eq. TMSI. Oxazolidinone opening typically required 4 to 6 hours. Subsequent elimination of HI was effected with 2.5 to 3 eq. DABCO overnight (ice bath). Then hydrolysis of the silyl carbamate and the resulting enamine by addition of 2.5 to 3 eq. of aqueous hydrochloric acid calculated to bring the pH to the isoelectric point resulted in the direct crystallization of pure carbacephem nuclei **15-19** (Equation 3). Yields in Equation 3 represent products that directly crystallized from the reaction mixture, and no attempt was made to optimize these conditions[11].



10	**X = Cl**	**15**	**X = Cl 70%**
11	**X = CF_3**	**16**	**X = CF_3 84%**
12	**X = OTf**	**17**	**X = OTf 21%**
13	**X = Br**	**18**	**X = Br 34%**
14	**X = I**	**19**	**X = I 33%**

Equation 3

The use of S-4-phenyl-2-oxazolidinone as both a chiral auxiliary and an N-protective group throughout the carbacephem synthesis results in a highly efficient preparation of this new class of antibacterials. When the methyl ester is used as a carboxyl protective group, simultaneous removal of both the methyl ester and the oxazolidinone with TMSI provides an even shorter synthesis.

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