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Chiral oxazolidinones as electrophiles: intramolecular cyclization reactions with carbanions and preparation of functionalized lactams

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ABSTRACT

The intramolecular cyclizations of oxazolidinones with carbanions adjacent to sulfones, sulfoxides, and phosphonates proceed in high yields to obtain functionalized γ and δ lactams. The chiral oxazolidinone precursors can be readily synthesized from commercial amino acids. The lactams from this study are useful synthetic intermediates, as demonstrated by the synthesis of a precursor for levetiracetam, an antiepileptic drug.

It is generally thought that carbamates are unreactive toward nucleophilic attack and it is this feature that has made them the protecting groups of choice for amines. Benzyloxycarbonyl and *t*-butoxycarbonyl derivatives of amines are extensively used in synthesis due to their stability when exposed to basic nucleophiles and ease of subsequent removal. In reality, carbamates can serve as electrophiles in certain situations and have more potential than appreciated in synthetic transformations.

The reactions of *N*-Boc amines with internal oxygen and nitrogen nucleophiles have been used extensively for the synthesis of heterocycles including oxazolidinones and imidazolidinones.[1] There have been some reports in the literature in which carbamates act as electrophiles upon treatment with carbanionic nucleophiles. For example, a general route to amides via treatment of carbamates of primary amines with highly basic Grignard reagents has recently been disclosed.[2] The reactions of carbamates with sulfonyl carbanions have been used to synthesize amidosulfones in good yields.[3] Similar reactions of carbamates with α-phosphono carbanions have also been reported.[4]

In contrast, there are only a few examples of intramolecular reaction of carbamates with carbon nucleophiles. The formal synthesis of the indole alkaloid deplancheine utilizing the cyclization of a phosphonate with an internal trichloroethyl carbamate is one particularly relevant example.[5] Previous research in our laboratory demonstrated that carbamate derivatives of aminosulfones undergo intramolecular cyclization upon treatment with strong base to give α-sulfonyl lactams.[6]

The last few decades have witnessed an explosion in the use of oxazolidinones, cyclic carbamates, as chiral auxiliaries.[7] Oxazolidinones, like their acyclic carbamates, have not been exploited as potential electrophiles in carbon–carbon bond forming reactions. In an interesting example, *N*-arylsulfonyl derivatives of oxazolidinones were found to undergo *ortho* or benzylic metalation. Intramolecular cyclization of the metalated intermediates on the oxazolidinone carbonyl led to the formation of various sulfamyl containing heterocycles including saccharins.[8] Intramolecular cyclization of an aryllithium on an oxazolidinone has been used to prepare isoindolinones.[9] Also, the intramolecular rearrangement of oxazolidinones to succinamides in the presence of base has been reported.[10]

As discussed, so far there has been very little interest in exploiting the electrophilic chemistry of oxazolidinones for synthetic purposes. A broad variety of chiral oxazolidinones can be readily accessed from commercially available amino acid starting materials.[11] In this Letter, we disclose the results of our study on the intramolecular cyclization reactions of chiral oxazolidinones with stabilized carbanions and their applications in the preparation of functionalized lactams.

We hypothesized that oxazolidinones such as those shown in Scheme 1 carrying sulfones, sulfoxides, and phosphonates should undergo deprotonation with LHMDS and then cyclize to give a bridged intermediate. Since oxygen is generally a better leaving group than nitrogen, the intermediate would collapse to give the lactam product. There was some question as to whether steric

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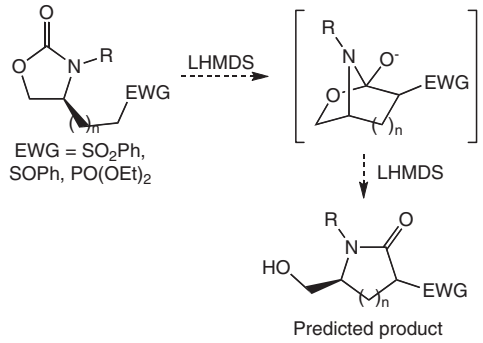


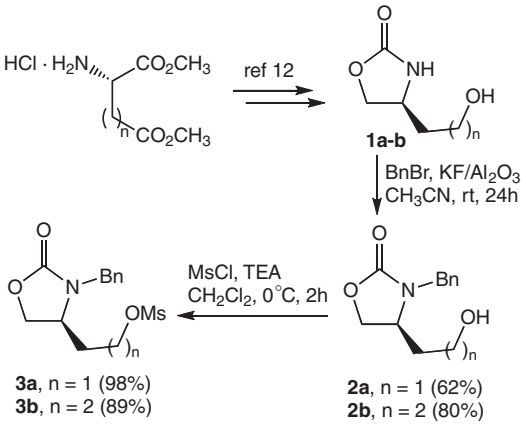
Scheme 1. Proposed cyclization reaction of oxazolidinones.

constraints would allow formation of the bicyclic intermediate in the intramolecular cyclization. One would expect the size of the newly generated ring to be critical for the success of this reaction.

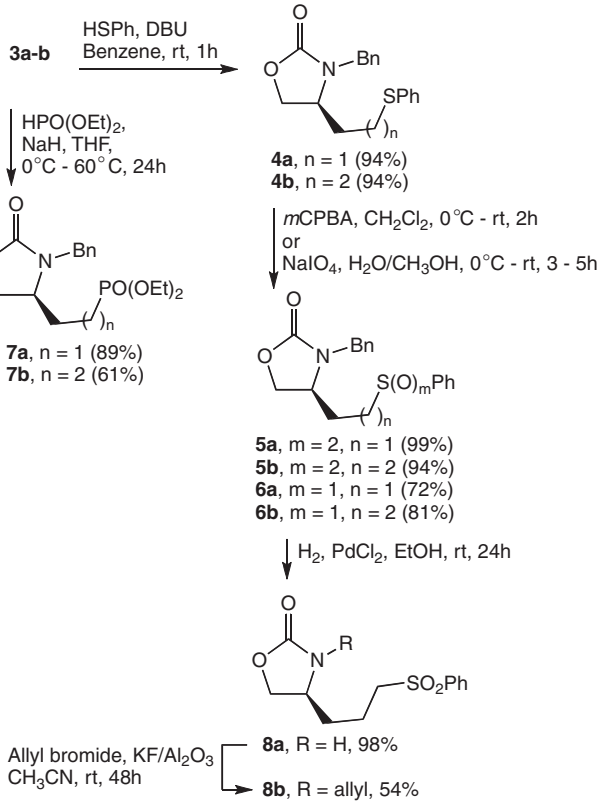
The requisite sulfonyl, sulfinyl, and phosphono oxazolidinones ($n = 1$) for the cyclization studies were conveniently accessed from alcohol **1a** which has been previously prepared from L-aspartic acid (Scheme 2).[12] The alcohol **1b** ($n = 2$) was prepared in a similar manner starting from L-glutamic acid. Selective N-benzylation of **1a–b** was achieved upon treatment of the substrates with benzyl bromide and KF/Al_2O_3. Subsequent treatment of *N*-benzyl oxazolidinones **2a–b** with methanesulfonyl chloride in the presence of triethylamine in DCM gave the corresponding mesylates **3a–b** in good yields.

The oxazolidinones **3a–b** were easily converted to the corresponding sulfonyl, sulfinyl, and phosphono derivatives (Scheme 3). Mesylates **3a–b** reacted with thiophenol in the presence of DBU in benzene to give phenyl sulfides **4a–b**. These were oxidized to give the sulfones **5a–b** and sulfoxides **6a–b** using *m*CPBA and $NaIO_4$, respectively. Reaction of the mesylates with the sodium salt of diethyl phosphite gave phosphonates **7a–b**. *N*-Allyl oxazolidinone **8b** was prepared for this study from the *N*-benzyl oxazolidinone **5b**, which was in hand. The oxazolidinone **5b** was debenzylated by hydrogenolysis in the presence of $PdCl_2$ to give **8a**, which was then treated with allyl bromide and KF/Al_2O_3 to give *N*-allyl oxazolidinone **8b**.

With oxazolidinones **5–8** in hand, their intramolecular cyclization reactions were examined. In a representative example, the sulfone **5a** was treated with LHMDS (2.1 equiv) in THF at −78 °C for 5 h and then the reaction mixture warmed to 0 °C for an additional hour. The reaction mixture was quenched with acetic acid and worked up using standard procedures. As predicted, the hydroxymethyl lactam **9a** was obtained as the major product (~40%) along with surprisingly some of its *O*-trimethylsilyl derivative (presumably formed by the silylation of the alkoxide of **9a** with hexamethyldisilazane under the reaction conditions). Subsequent reactions were worked up with 2 N HCl in order to isolate only the desired product. With this change in work up, the yield of the cyclization improved dramatically to give **9a** in a yield of 95% after chromatographic purification. Using the same reaction protocol, the intramolecular cyclizations of the other sulfonyl, sulfinyl, and phosphono oxazolidinone derivatives **5–8** were found to proceed in excellent yields (Table 1).[13]



Scheme 2. Synthesis of mesylates **3a** and **3b**.



Scheme 3. Synthesis of sulfone, sulfoxide, and phosphono oxazolidinones **5–8**.

The intramolecular cyclization of oxazolidinones provided access to a variety of functionalized chiral lactams. The chemistry of the sulfoxide and phosphonate lactams was of particular interest as they have the potential to be valuable synthetic intermediates. When sulfoxide lactams **9c** and **9d** were heated at 100 °C in the presence of PPh_3 on polystyrene, α,β-unsaturated lactams **10a** and **10b** were obtained in good yields after chromatography (Scheme 4). It is important to note that stereoselective 1,4-additions to α,β-unsaturated lactams have found much use in the synthesis of biologically active targets.[14,15] Indeed, the stereoselective 1,4-addition of an aryl cuprate to the O-silylated *N*-Boc analog of **10a** has been used in the asymmetric synthesis of (*R*)-(−)-Rolipram, a potent inhibitor of cardiac cyclic AMP phosphodiesterase,[16] and (*R*)-Baclofen, a derivative of the inhibitory neurotransmitter GABA.[17] It is our belief that the ready availability of **10a** and **10b** should allow preparation of some drugs of interest and their analogs.

It was also of interest to study the Horner–Wadsworth–Emmons (HWE) reactions of phosphonolactams **9e** and **9f**. Lactam **9e** was treated with propionaldehyde in the presence of DBU and LiCl to give the α,β-unsaturated lactam which was subjected to Pd/C catalyzed hydrogenation giving **11a** in 56% yield after column