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COMMUNICATION

A Lewis acid initiated intramolecular cyclization of benzylidene acetal with an azide functional group: novel synthesis of oxazolines and oxazines†

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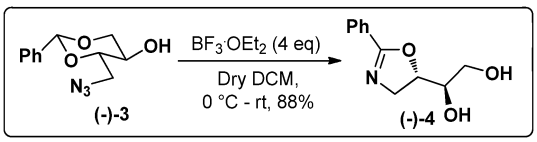
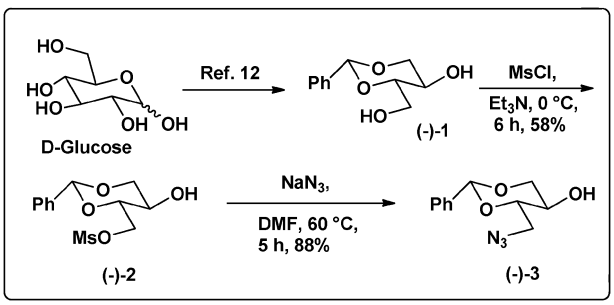
Stereoselective synthesis of 2-phenyl-oxazolines and 2-phenyl-oxazines *via* Lewis acid initiated intramolecular cyclization of benzylidene acetal with an azide functional group is described.

In recent years, oxazolines and oxazines have been considered as a very interesting class of heterocycles with wide range of applications in synthetic organic chemistry. Oxazolines are frequently found in biologically active natural products and pharmaceuticals exhibiting cytotoxic, neuroprotective, antibiotic and antifungal properties.[1] In addition, 2-oxazoline moieties serve as hydrolysable precursors for carboxylic acids in prodrugs and also as templates in organic synthesis.[2] In recent years, oxazoline ring systems, especially C_2-symmetric bis-oxazolines (box's), have received a great deal of attention as chiral ligands in coordination chemistry for inducing high enantioselectivity.[3–5] As a consequence of their wide ranging applications, many synthetic methods towards the synthesis of oxazolines have been reported in the literature.[6] Generally oxazolines are prepared by the reaction of β-aminoalcohols with nitriles, acid chlorides, esters, carboxylic acids, imino ethers, alkyl imidates and acyl benzotriazoles.[7] Other methods such as (i) reaction between aldehyde and hydroxy azide and (ii) cyclization of hydroxy amides using the Burgess-reagent, diethylaminosulfur trifluoride (DAST), PPh_3/DIAD, diisopropylcarbodiimide (DIC)/$Cu(OTf)_2$ and immobilised *p*-toluenesulfonyl chloride/Et_3N have also been reported.[8]

Recently, we developed a novel method for the direct oxidation of benzylidene acetals to α- and β-benzoyloxy carboxylic acids in one pot. This methodology was further exploited in the enantioselective synthesis of α-benzoyloxy carboxylic acids from terminal olefins.[9] Our enduring interest in exploring the synthetic potential of benzylidene acetals in organic synthesis resulted in the development of highly chemo- and regioselective methods for the cleavage of benzylidene acetals under mild reaction conditions.[10]



Scheme 1 Synthesis of 2-phenyl-oxazoline *via* intramolecular cyclization of benzylidene acetal with an azide functional group.



Scheme 2 Synthesis of benzylidene acetal **3** from D-glucose.

In this communication, we report a novel intramolecular cyclization of benzylidene acetal with an azide functional group[11] which resulted in the stereoselective synthesis of 2-phenyl-oxazolines and 2-phenyl-oxazines in good yields.

Interestingly, compound (−)-**3** on treatment with $BF_3{\cdot}OEt_2$ (4 eq) in dry DCM underwent smooth Lewis acid initiated intramolecular Schmidt type cyclization in a remarkable manner to give the corresponding cyclized product (−)-**4** in good yield (Scheme 1). Compound (−)-**3** was prepared starting from D-glucose *via* intermediate (−)-**1**[12] as shown in Scheme 2.

Moreover the structure and stereochemistry of the cyclized product (−)-**4** were unambiguously confirmed by single crystal X-ray analysis (Fig. 1).[13]

This unusual transformation was further studied with various benzylidene acetals having sensitive functional groups and the results are summarized in Table 1. The benzylidene acetals having the azido-methyl group at the alpha position underwent smooth cyclization to give the corresponding 2-phenyl-oxazolines in good yields (Table 1, entries 1 and 2). Similarly, benzylidene acetals having the azido-methyl group at the beta position reacted readily under these conditions to give the corresponding 2-phenyl-oxazines in good yields (Table 1, entries 3–5). Moreover, under the reaction conditions,

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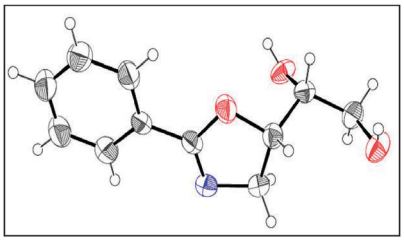
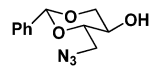
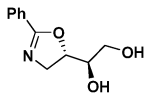
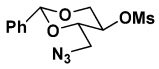
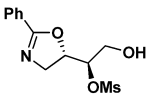
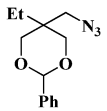
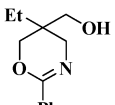
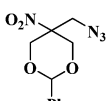
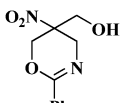
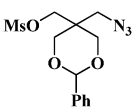
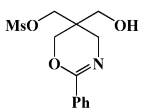
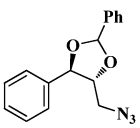
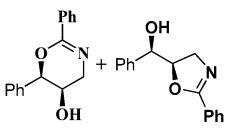
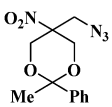


Fig. 1 ORTEP diagram of 2-phenyl-oxazoline (−)-**4**.

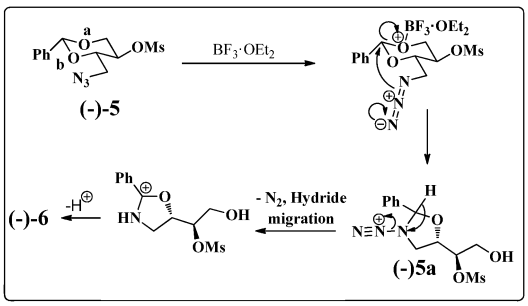
Table 1 Cyclization of benzylidene acetal with an azide functional group

Entry	Substrate	Time/h	Product	Yield (%)[a]
1	 (-)-3	3.5	 (-)-4	88
2	 (-)-5	3	 (-)-6	85
3	 7	5	 8	68
4	 9	4.5	 10	65
5	 11	5	 12	69
6	 (±)-13	4	 (±)-14 (4:1) (±)-15	75
7	 16	24	No reaction	—

[a] Isolated yield.

the azido-benzylidene acetal (±)-**13** underwent smooth cyclization to give the corresponding 2-phenyl-oxazine (±)-**14** as a major product in 60% yield whereas the 2-phenyl-oxazoline (±)-**15** was isolated in 15% yield. Interestingly, the functional groups such as OH, –OMs, and –NO_2 are found to be stable under the reaction conditions.

A plausible mechanism for the cyclization of benzylidene acetal with azide leading to the formation of 2-phenyl-oxazoline is shown in Scheme 3. It is anticipated that $BF_3{\cdot}OEt_2$ would



Scheme 3 Plausible mechanism for the intramolecular cyclization of benzylidene acetal with an azide functional group.

initially coordinate with the less hindered oxygen atom (**a**) of the benzylidene acetal (−)-**5**, thus creating a partial polarization followed by intramolecular attack by the azide group at the benzylic carbon leading to the amino-diazonium ion intermediate (−)-**5a**. The resultant intermediate (−)-**5a** on 1,2-hydride shift coupled with nitrogen expulsion[8g] and subsequent proton loss would result in the formation of the corresponding 2-phenyl-oxazoline (−)-**6**.

As expected, azido-benzylidene acetal **16** under the same reaction conditions failed to give any cyclized product, which further supports the proposed mechanism.

In conclusion, a mild and efficient method has been developed for the synthesis of oxazolines and oxazines *via* $BF_3{\cdot}OEt_2$ mediated intramolecular cyclization of benzylidene acetal with an azide functional group. Salient features of this methodology are mild reaction conditions and the reaction proceeds without any racemization of the chiral center. We hope this novel methodology will find wide application in organic synthesis.

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13 CCDC 670499 contains the supplementary crystallographic data for this paper.

