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NOVEL FRAGMENTATION OF 3-LITHIO-3,6-DIHYDRO-1,2-OXAZINES: SYNTHESIS OF 2,5-DIHYDRO-2-FURANYLAMINES

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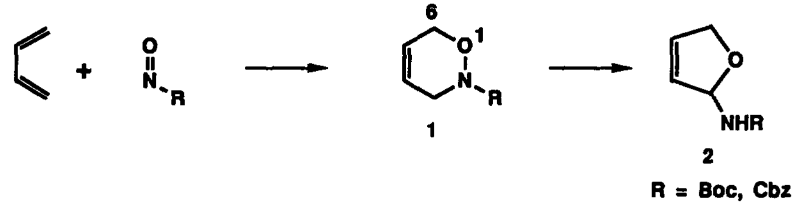
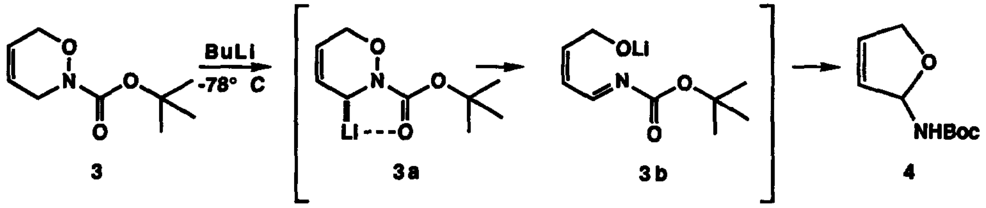
Abstract: N-Cbz or N-Boc protected 3,6-dihydro-1,2-oxazines **1** on treatment with LDA at -78°C undergo a novel rearrangement to provide synthetically useful N-Cbz or N-Boc protected dihydro-2-furanylamines **2**.

A wide variety of nitroso compounds participate as dienophiles in *Diels-Alder* reactions with conjugated 1,3-dienes to afford 3,6-dihydro-1,2-oxazines (**1**)[1]. The use of N-hydroxycarbamic esters in the above reaction affords oxazine derivatives having readily removable N-protecting groups (e.g. Cbz or Boc)[2]. One of most useful synthetic applications of 3,6-dihydro-1,2-oxazines **1** is the reductive cleavage of the nitrogen-oxygen bond to generate a 1,4-bifunctional group in *syn* orientation; many groups have creatively used the latter reaction as a key step in the total synthesis of numerous natural products[3]. We report another potentially useful reaction of 1,2-oxazines **1** (R=Boc or Cbz) to provide 2,5-dihydro-2-furanylamines **2**[4].

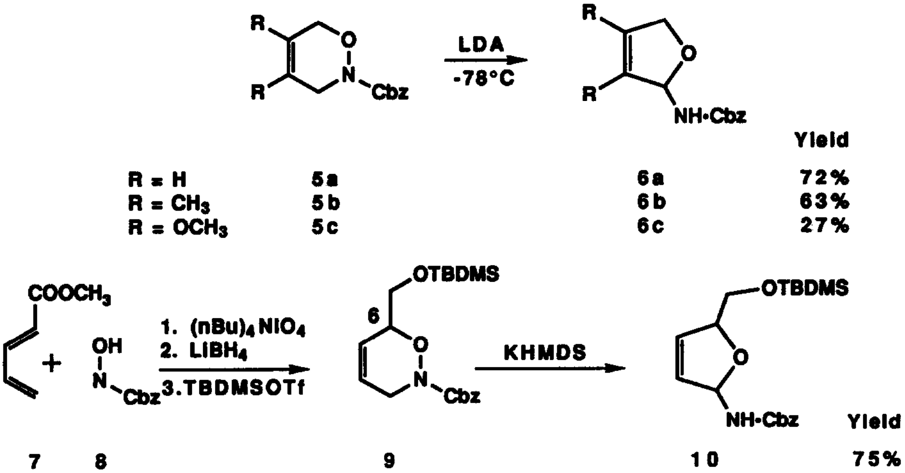




We planned to generate anion **3a**, and then quench it with an appropriate electrophile[5]. Interestingly, treatment of **3** with *n*-butyl lithium in hexane/THF at -78° C afforded **4**. The formation of **4** implies the initial generation of **3a**, which fragments to form the γ-oxido-α,β-unsaturated N-Boc-imine **3b**. The Z-stereochemistry of the double bond in **3b** favors subsequent intramolecular addition of the γ-oxido anion to yield **4**. The ease with which 3,6-dihydro-1,2-oxazines can be synthesized in a regioselective manner suggests that the above reaction could be of synthetic value[1,6]. The ring contraction reaction was investigated on several N-Cbz oxazines **5a-c**. After extensive experimentation, we established that treatment of **5a-c** with 2.0 equivalent of LDA in THF at -78°C afforded **6a-c**; Fig. 1 summarizes our experimental results.

An important aspect of the rearrangement is possible diastereoselectivity with oxazines such as **9** which contain an asymmetric center at C-6. To investigate this, **9** was synthesized *via* a three-step process: (1) *Diels-Alder* reaction of methyl sorbate (**7**) and benzylnitrosoformate (generated *in situ* by oxidation of **8** with tetrabutyl ammonium periodate); (2) reduction of carboxymethyl group to hydroxymethyl with lithium borohydride; and (3) protection of the hydroxy group as its TBDMS ether. Treatment of **9** with LDA at -78° C afforded **10** in 75% yield after chromatographic purification, as a 1:1 mixture of two diastereoisomers. The presence of a methine proton at C-2 in the ^{1}H-NMR of **10** clearly supports the regiochemistry shown in **9** for the *Diels-Alder* reaction[3e].

Fig. 1. Synthesis of N- Cbz-2,5-dihydro-2-furanylamines from 3,6-dihydro-1,2-oxazines:



The combination of ease of synthesis of substituted oxazines, and their base-induced rearrangement described in this paper may provide an alternate route for the synthesis of 2,5-dihydro-2-furanyl amines from non-carbohydrate intermediates. The possibility of being able to perform the rearrangement asymmetrically may further enhance the utility of the reaction.

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