SYNLETT
Spotlight 251

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

N-Benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde Nitrone

Compiled by Gabriel Podolan

Gabriel Podolan was born in Myjava, Slovak Republic, in 1983. He studied chemistry at the Slovak University of Technology in Bratislava and obtained his M.Sc. in 2007. Also in 2007, he spent three months in the group of Prof. Reissig at the Freie Universität Berlin, Germany, where he was involved in a project on alkoxyallenes. He is now working on his Ph.D. thesis under the supervision of Prof. L. Fišera at the Slovak University of Technology in Bratislava. His current research is focused on cycloadditions of chiral nitrones with methylacrylate and the use of cycloadducts in the synthesis of indolizidine and pyrrolizidine derivatives.

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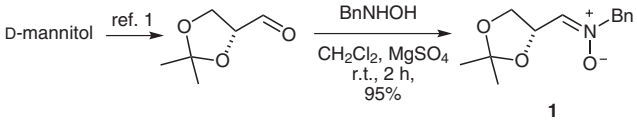
Introduction

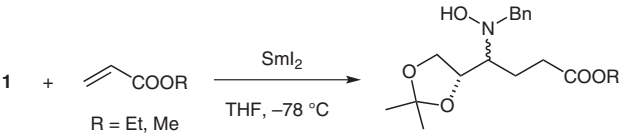
N-Benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde nitrone (**1**; Scheme 1) is a highly flexible compound that can be used as reagent in a number of addition reactions, [3+2] cycloadditions, and the new [3+3] cyclization leading to chiral nitrogen-containing acyclic and cyclic products. The enantiopure nitrone can be prepared by a very effective route from the readily available D-mannitol. Starting with a regioselective ketalization, oxidative diol cleavage of the resulting glycol results in the D-glyceraldehyde precursor.[1] Treatment of this aldehyde with *N*-benzylhydroxylamine in the presence of $MgSO_4$ gives nitrone **1** in excellent yield.[2]



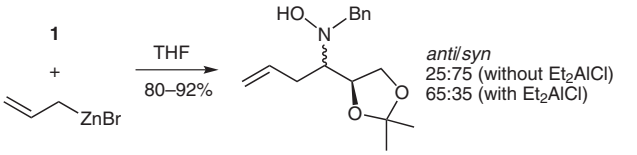
Scheme 1

Abstracts

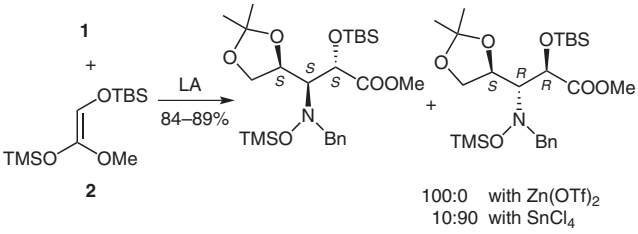
(A) The SmI_2-mediated reaction of nitrone **1** with ethyl or methyl acrylate led in fairly good yields to the expected γ-*N*-hydroxyamino esters;[3] in both cases, the *anti* configuration was preferred. The *anti*-configured methyl ester product is a known intermediate in the synthesis of (*S*)-vigabatrin.[3,4]



(B) Allylzinc bromide regioselectively added to **1** in very good yield,[5] whereby homoallylic hydroxylamines were observed with different stereoselectivities depending on the presence or the absence of Et_2AlCl. A slightly higher diastereofacial *anti*-selectivity was observed with allylzinc bromide than with the previously reported allylmagnesium chloride.[6]



(C) The Mannich-type reaction of nitrone **1** and 2-silyloxy silyl ketene acetal **2** was performed with high stereocontrol to give the resulting adducts in good yields.[7] When the addition was performed in the presence of $Zn(OTf)_2$, the (2*S*,3*S*,4*S*)-configured product was formed as single isomer, whereas the use of $SnCl_4$ led to the (2*R*,3*R*,4*S*)-configured isomer with high preference.



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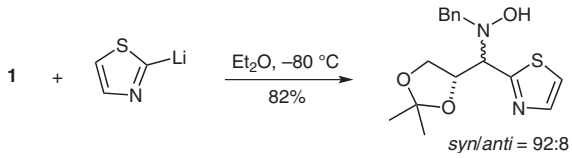
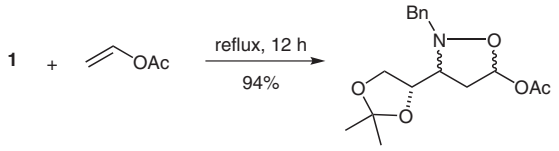
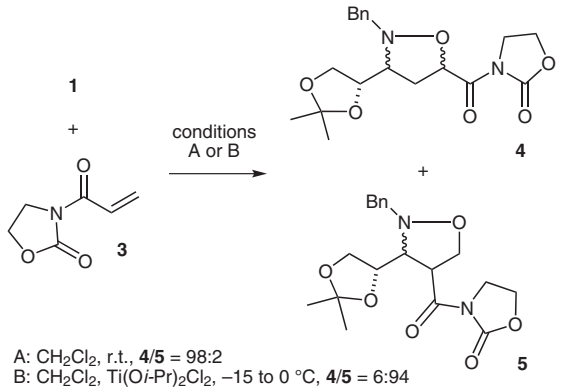
(D) The reaction of **1** with 2-lithiothiazole produced the expected hydroxylamine adduct in good yield and with very high *syn*-selectivity.[8]



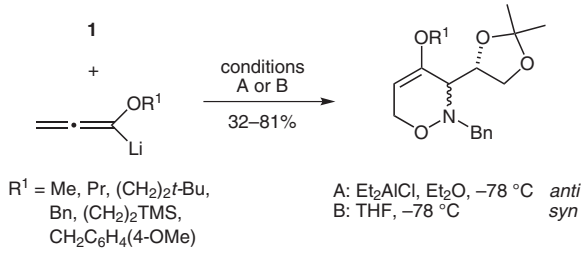
(E) Nitrone **1** was utilized in the synthesis of nucleoside analogues. The methodology[9] consists of the 1,3-dipolar cycloaddition of **1** with either vinyl acetate or related compounds to give key intermediates that are easily converted into target compounds.[10]



(F) The regioselectivity of the cycloaddition of **1** with alkene **3** depends on the nature of the Lewis acid catalyst used, where the presence or the absence of Lewis acid can reverse the regioselectivity.[11] The sterically favored isoxazolidin-5-yl substituted adduct **4** is produced as the major product in the absence of Lewis acid, while the electronically favored regioisomer **5** is obtained when the reaction is performed in the presence of Lewis acid.



(G) Addition of lithiated alkoxyallenes[12] to nitrone **1** provided, in a formal [3+3] cyclization, 4-alkoxy-1,2-oxazines in good yields and with excellent *syn*-selectivity.[13] A complete switch to the *anti*-configured 1,2-oxazines was achieved by precomplexation of **1** with Et_2AlCl. The *syn*- and *anti*-configured 1,2-oxazine products are ideal precursors for stereoselective syntheses of a variety of nitrogen-containing compounds.[14]



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