SYNLETT Spotlight 251

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

Compiled by Gabriel Podolan

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

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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 MgSO₄ gives nitrone **1** in excellent yield.²

Scheme 1

Abstracts

(A) The SmI₂-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 Et₂AlCl. 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 SnCl₄ led to the (2*R*,3*R*,4*S*)-configured isomer with high preference.

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

(E) Nitron **1** was utilized in the synthesis of nucleoside analogues. The methodology⁹ 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 alkoxyallenes¹² to nitron **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 Et₂AlCl. The *syn*- and *anti*-configured 1,2-oxazine products are ideal precursors for stereoselective syntheses of a variety of nitrogen-containing compounds.¹⁴

References

- (1) Schmid, C. R.; Bryant, J. D.; Dowlatzadeh, M.; Phillips, J. L.; Prather, D. E.; Schantz, R. D.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.* **1991**, *56*, 4056.
- (2) (a) DeShong, P.; Dicken, C. M.; Leginus, J. M.; Whittle, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 5598. (b) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F.; Merino, P.; Tejero, T. *Synth. Commun.* **1994**, *24*, 2537.
- (3) (a) Masson, G.; Cividino, P.; Py, S.; Vallée, Y. *Angew. Chem. Int. Ed.* **2003**, *42*, 2265; *Angew. Chem.* **2003**, *115*, 2367. (b) Masson, G.; Zeghida, W.; Cividino, P.; Py, S.; Vallée, Y. *Synlett* **2003**, 1527.
- (4) Alcón, M.; Poch, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2967.
- (5) Fiumana, A.; Lombardo, M.; Trombini, C. *J. Org. Chem.* **1997**, *62*, 5623.
- (6) Dhavale, D. D.; Gentilucci, L.; Piazza, M. G.; Trombini, C. *Liebigs Ann. Chem.* **1992**, 1289.
- (7) Merino, P.; Jimenez, P.; Tejero, T. *J. Org. Chem.* **2006**, *71*, 4685.
- (8) Dondoni, A.; Franco, S.; Merchán, L. P.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1993**, *34*, 5475.
- (9) Merino, P.; del Alamo, E. M.; Franco, S.; Merchan, F. L.; Simon, A.; Tejero, T. *Tetrahedron: Asymmetry* **2000**, *11*, 1543.
- (10) Vorbrüggen, H.; Krolkiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.
- (11) Dugović, B.; Fišera, L.; Cyranski, M. K.; Hametner, C.; Pronayova, N.; Obranec, M. *Helv. Chim. Acta* **2005**, *88*, 1432.
- (12) (a) Zimmer, R. *Synthesis* **1993**, 165. (b) Zimmer, R.; Reissig, H.-U. *Donor-Substituted Allenes*, In *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, **2004**, 425. (c) Reissig, H.-U.; Zimmer, R. In *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*, Vol. 44; Krause, N., Ed.; Thieme: Stuttgart, **2008**, 301.
- (13) Helms, M.; Schade, W.; Pulz, R.; Watanabe, T.; Al-Harrasi, A.; Fišera, L.; Hlobilová, I.; Zahn, G.; Reissig, H.-U. *Eur. J. Org. Chem.* **2005**, 1003.
- (14) (a) Reissig, H.-U.; Hormuth, S.; Schade, W.; Okala Amombo, M.; Watanabe, T.; Pulz, R.; Hausherr, A.; Zimmer, R. *J. Heterocycl. Chem.* **2000**, *37*, 597. (b) Brasholz, M.; Reissig, H.-U.; Zimmer, R. *Acc. Chem. Res.* in press.