Tetrahedron Letters,Vol.30,No.45,pp 6139-6142,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SILYL NITRONATES IN CARBOHYDRATE CHEMISTRY: CHAIN-EXTENSION REACTIONS

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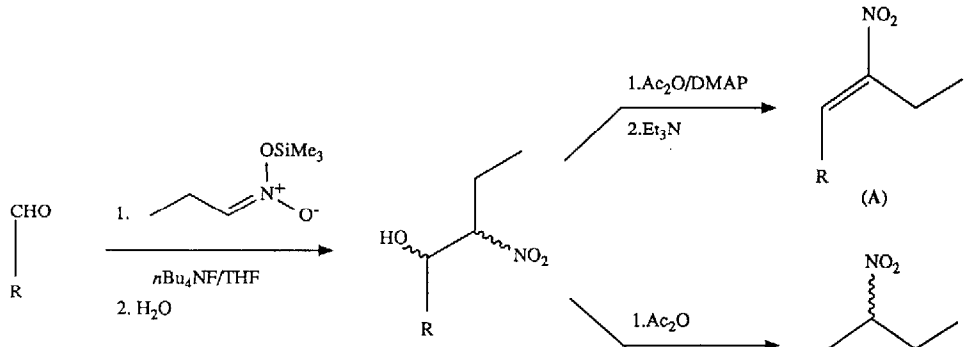
Abstract: Seebach's silyl nitronate nitroaldol methodology provides a highly efficient variation of the Henry reaction for the chain-extension of *aldehydo*-sugars to higher nitro sugars under extremely mild conditions.

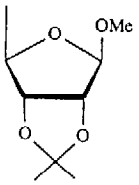
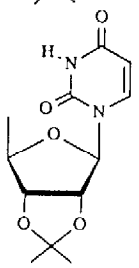
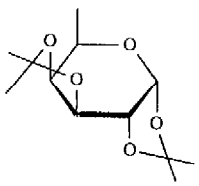
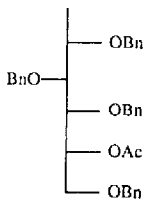
The base-catalyzed condensation of nitroalkanes with *aldehydo*-sugars (Henry reaction) constitutes one of the most common methods of extension of the carbohydrate carbon chain.[1,2] As a result of the very mild reactivity of the nitronate anion, this method has been applied successfully to the synthesis of highly complex carbohydrate structures such as, for example, the undecodiose component of the tunicamycins[3] or the nucleoside antibiotic sinefungin.[4-6] In the course of our studies on the synthesis of pseudodisaccharides, we had to deal with the problem of coupling two base-sensitive sugar units by way of a nitroaldol reaction. We considered that the desired coupling could be achieved under even milder and very specific conditions using the novel version of the nitroaldol process recently described by Seebach *et al.*,[7] namely the fluoride-ion catalyzed condensation of silyl nitronates with aldehydes. In order to establish that Seebach's nitroaldol methodology is applicable to carbohydrate derivatives, the reactivity of *aldehydo*-sugars with silyl nitronates as well as of sugar-derived silyl nitronates with aldehydes was investigated. We wish to report, in this communication and the following one, the results of these studies on model compounds.

A series of representative *aldehydo*-sugars, including a 5'-*aldehydo*-nucleoside (see Table) were reacted with 1-*aci*-nitropropane trimethylsilyl ester[8] (1.1 equiv.) in THF for 3 h at -78°C and 12 h at room temperature, in the presence of a catalytic amount of fluoride ion (as nBu$_4$NF); after dilution with ether, the reaction mixture was processed with water[9] and the nitroaldols were isolated by column chromatography. In all cases the adducts were obtained as mixtures of diastereoisomers in good to excellent yield, which demonstrate that the silyl nitronate nitroaldol methodology is highly efficient in the carbohydrate series. The success of the process in the case of *aldehydo*-uridine derivative **5** is particularly remarkable and is clearly due to the extremely mild conditions of the condensation: chain-extensions of related sensitive *aldehydo*-nucleosides with higher nitroalkanes have been indeed characterized by lower yields.[5,10] Furthermore, by contrast to the standard Henry reaction conditions, the condensation does not require a

TABLE

Reactions of *Aldehydo*-sugars with 1-*aci*-nitropropane trimethylsilyl ester (isolated yields)

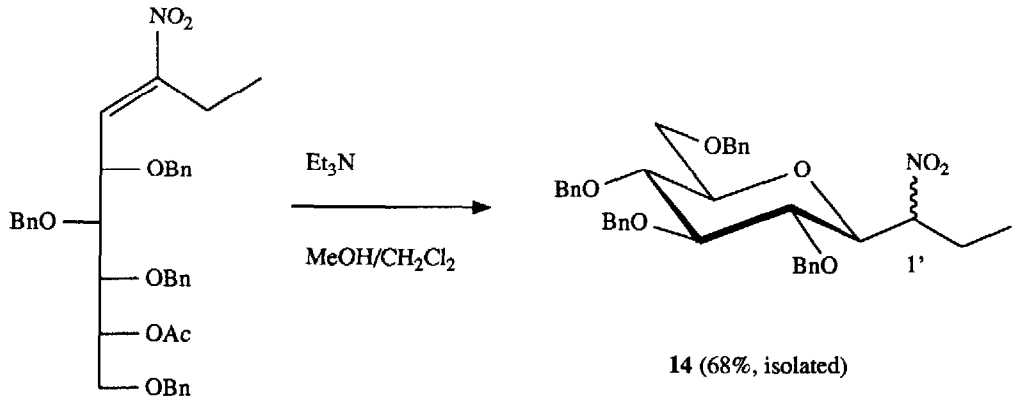


R	CHO | R		
	1 (Ref. 13,15)	2 (74%)	(A) 3 (48%) (B) 4 (73%)
	5 (Ref. 14)	6 (65%)	(A) 7 (48%)
	8 (Ref. 15)	9 (63%)	(B) 10 (54%)
	11 (Ref. 16)	12 (75%)	(A) 13 (60%)

large excess of the nitroalkane component (in this case the silyl nitronate), which represents a major advantage of this methodology.

As tests for further transformations required in our synthetic programs, the nitroaldols were elaborated either by acetylation-elimination (procedure A,[11] see Table), to give the corresponding nitroalkenes (**3**, **7**, and **13**), or by acetylation-selective hydrogenation (procedure B,[12] see Table), to lead to the corresponding β-deoxygenated nitrosugars (**4**, **10**). The nitroalkenes were formed almost exclusively with the *E* configuration (*E*:*Z* >95:5), the chemical shift of the vinylic proton (*E* isomers: δ =CH 7.0 — 7.2; *Z*-isomer: 5.8 — 6.0 ppm) clearly establishing the configuration of the trisubstituted double bond of compounds **3**, **7**, and **13**.

Nitroalkene **13**, derived from open-chain *aldehydo*-glucose derivative **11** was of particular interest as a precursor of a *C*-glycosidic structure: the stereoselective cyclization of nitroalkene **13** into a *C*-glucopyranosyl nitroalkane was achieved very effectively upon deacetylation of the selectively acetylated hydroxyl function of the substrate under mildly basic conditions (MeOH-H_2O-Et_3N, 8:2:1). As expected, the "*C*-glycoside" (compound **14**) was formed exclusively with the thermodynamically more favorable β-configuration (no α-anomer detected), and as a mixture of stereoisomers at C-1'. This approach is now being applied to the synthesis of disaccharide analogs.



13

14 (68%, isolated)

Ratio of isomers at C-1': 2:1

Acknowledgment. Support from the National Institutes of Health for this research (Grant DK35766) and from the U. S. Department of Education for the purchase of a high-field NMR spectrometer (Grant 2-20-1009) is gratefully acknowledged.

References and Notes

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9. The intermediate silyl ethers obtained from **11** were cleaved by brief treatment of the adducts in methanol containing Amberlite IR-120(H^+) ion-exchange resin, at reflux temperature. However, this step may not be necessary since the silyl ethers are cleaved on silica gel during the isolation process.
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11. Typical conditions: acetylation with acetic anhydride (excess) in ether in the presence of 1 equiv. of 4-*N*,*N*-dimethylaminopyridine; elimination using triethylamine in ethyl acetate.
12. Typical conditions: slow addition of a solution of acetylated nitroaldol in ethanol to a cold suspension of $NaBH_4$ in ethanol.
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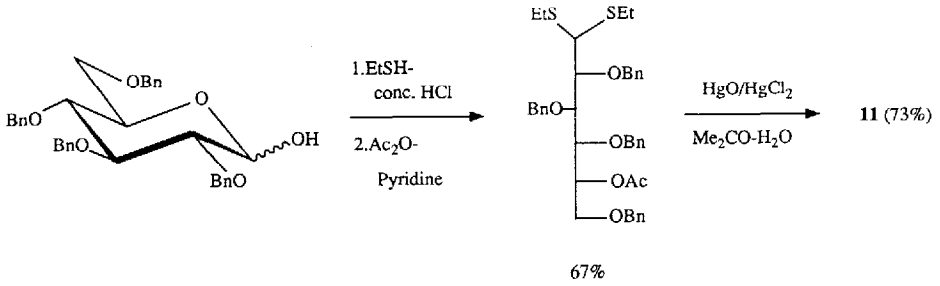
16. *Aldehydo*-glucose derivative **11** was prepared as follows:



(Received in USA 7 June 1989)