Pergamon

*Tetrahedron Letters*, Vol. 37, No. 35, pp. 6279-6282, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01376-7

# Molecular Sieves Promote Stereocontrolled αα-Disaccharide Formation *via* Direct Dimerization of Free Sugars

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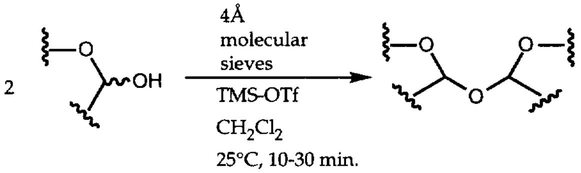
*Abstract:* Some commercial molecular sieves promote direct dimerization of free pyranose and furanose sugars stereoselectively into the corresponding α,α-disaccharides.

Our interest in glycoside bond formation[1] and in organic reactions promoted by porous solids[2-6] brought to our attention a recent report involving molecular sieves in disaccharide formation.[7] We have found now that some zeolites are especially effective and convenient to use in promoting stereoselective α,α-disaccharide formation *via* direct dimerization of various pyranose and furanose free sugars, characterized by an unactivated anomeric hydroxyl group (Eq. 1). Some α,α-disaccharides (*e.g.* trehalose) are ubiquitous and biologically important compounds found naturally as mycobacterial glycolipids that have both toxic properties as well as medicinal value as antitumor and immunostimulant compounds.[8] Methods for stereocontrolled synthesis of α,α-disaccharides, however, have been of variable success.[7,9-15]



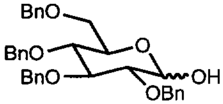
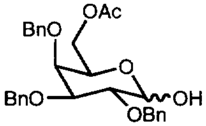
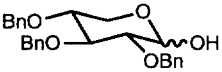
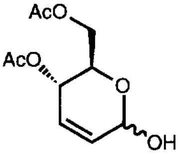
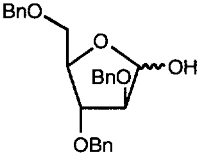
(1)

Although many organic synthesis procedures involve molecular sieves,[16-18] most often as a scavenger for water,[19] the nature and hydration level of such zeolites are seldom considered explicitly. Nevertheless, molecular sieve hydration has been reported to affect the diastereoselectivity of palladium-catalyzed cyclization of 1,2-divinylcyclohexane with chiral carboxylic acids[20] as well as the enantioselectivity of some asymmetric Diels-Alder cycloadditions.[6] Also, the presence of sieves has been reported to raise the yields in some asymmetric aziridination reactions,[21] and the timing of when sieves are added to a reaction mixture has been reported to influence the stereochemical outcome of asymmetric titanium-promoted oxidations of sulfides into sulfoxides.[22,23]

The recent Japanese report that molecular sieves (of unspecified origin) are crucial for the successful formation of 1,1'-disaccharides directly from 1-hydroxy sugars using trimethylsilyl triflate (TMS-OTf) as promoter[7] as well as our recent interest in zeolites[6] prompted us to investigate the effect of the **source** and **hydration level** of the sieves on this important carbohydrate dimerization reaction. After examining commercial 4Å molecular sieves, each of about 16% water content, from Aldrich, Janssen, Lancaster and Davison Chemical Companies, we found that commercial Davison SP 7-8461 sieves gave **by far** the best results; varying the water content of these sieves from 2.5-16% gave no significantly different results. Different batches of the Davison SP 7-8461 sieves gave the same dimerization results. Therefore, our routine procedure involved use of the commercial Davison SP 7-8461 sieves having about 3% water content directly as received. The most noteworthy differences between the Davison zeolites and the others are the significantly lower concentrations of calcium oxide and magnesium oxide and the significantly higher concentrations of ferric oxide, sodium oxide and sulfate ions in the Davison zeolites.[24] The Davison molecular sieves were not the most caustic, nor did they differ much from the other zeolites in terms of $Al_2O_3$ or $SiO_2$ content. At this time, it is not clear which (if any) of these variables is most important for the observed high α,α-selectivities.

The following features of the results summarized in Table 1 using optimized amounts of TMS-OTf are especially noteworthy: (1) simply by changing the nature of the zeolite, we have shown that considerably higher α,α-selectivities can be achieved relative to the literature report[7] in formation of the protected α,α-trehalose 1,1'-disaccharide in entry 1; (2) likewise for entry 2, the stereochemical α,α-selectivity is much higher than that reported previously;[7,25] (3) although the two results for the unsaturated pyranose in entry 4 are similar, the literature procedure[25] involves coupling of two **different** pyranoses, the anomeric acetate of the pyranose free sugar shown in entry 4 and the corresponding glucal; (4) although the two results for the furanose in entry 5 are similar, the literature procedure[26] requires use of phosgene to pre-form a reactive alkylating iminium ion to activate the anomeric hydroxyl group; and (5) the results in gram-scale dimerizations for entries 1 and 5 (and presumably also for all of the other entries) are essentially the same as in the 100 milligram-scale reactions shown in Table I. A control reaction showed that all of the trehalose 1,1'-disaccharides diastereomers in entry 1 were stable to the reaction conditions. Thus, this heterogeneous zeolite procedure offers a simple, convenient, direct and environmentally friendly method for α,α-selective dimerization of some free pyranose and furanose sugars, and these results underscore the importance of the source and the nature of the zeolite for optimum α,α-stereocontrol.

**Table 1. 1,1'-Disaccharide Formation**

| Entry | Sugar | 1,1'-Disaccharide (ratios) | | | % yield | TMS-OTf (equiv) | Comments |
|---|---|---|---|---|---|---|---|
| | | αα- | αβ- | ββ- | | | |
| 1 |  | 2.8 | 1.0 | 0.1 | 76 | 2.0 | this work |
| | | 1.8 | 4.0 | 1.0 | 75 | 2.0 | Ref. 7 |
| 2 |  | 7.8 | 1.0 | -- | 47 | 1.5 | this work |
| | | 1.2 | 1.0 | -- | 35 | 1.5 | Ref. 7 |
| 3 |  | 3.0 | 1.0 | -- | 34 | 1.0 | this work |
| | | 2.4 | 1.0 | -- | 38 | 1.5 | Ref. 7 |
| 4 |  | only | -- | -- | 36 | 0.25 | this work |
| | | only | -- | -- | 44 | | Ref. 25 |
| 5 |  | only | -- | -- | 62 | 1.0 | this work |
| | | only | -- | -- | 70 | | Ref. 26 |

We hope that publication of these results will further emphasize to the organic chemistry community that the choice of a particular molecular sieve may have a profound effect on the outcome of some chemical reactions.[27,29]

**Acknowledgments:** We thank the NSF (CHE-9321256) for financial support and the W.R. Grace & Co., Columbia, MD, for help in characterizing the various zeolites.

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24. Analysis of commercial 4Å molecular sieves showed the following components:

| Chemical | Davision | Aldrich | Janssen | Lancaster |
|---|---|---|---|---|
| CaO | 0.061 | 0.083 | 0.098 | 0.074 |
| MgO | 0.010 | 0.023 | 0.018 | 0.023 |
| $Fe_2O_3$ | 0.044 | 0.022 | 0.020 | 0.029 |
| $Na_2O$ | 22.815 | 22.290 | 22.057 | 22.416 |
| $SO_4^{-2}$ | 0.035 | 0.029 | 0.022 | 0.027 |

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26. Dourtoglou, V.; Gross, B. *J. Carbohydr. Chem.* **1983**, *2*, 57.
27. 2,3,4,6-Tetra-O-benzyl-D-glucopyranose (1.00 g, 1.85 mmoles) and 4Å Davison SP 7-8461 molecular sieves (500 mg, 2.9% water content[6]) were weighed into a dry, argon-filled 50 mL round bottom flask containing a teflon-coated magnetic stirring bar. $CH_2Cl_2$ (20 mL distilled from $CaH_2$) was added *via* an argon-flushed syringe. The reaction mixture was stirred for 15 minutes to allow complexation of the sugar onto the sieves. Trimethylsilyl trifluoromethanesulfonate (717 µL, 3.70 mmoles) was then added dropwise *via* an argon-flushed syringe. After analytical tlc indicated that the starting sugar was no longer present (~30 minutes), the reaction was quenched with 20 mL of saturated $NaHCO_3$, followed by extraction with 3 x 150 mL portions of $Et_2O$. The extracts were dried over Mg $SO_4$, filtered through Celite® and concentrated. Stereoselectivity was determined by integration of the $^{13}$C-NMR signals for the acetal carbons[28] (αα: 94.4 ppm, J=169 Hz; α of αβ: 99.5 ppm, J=171 Hz; β of αβ: 104.1 ppm, J=160 Hz; ββ: 99.3 ppm, J=163 Hz) in the crude product mixture, and this method was confirmed by normal phase HPLC analysis. Column chromatography gave the pure disaccharide products αα (481 mg, 49% yield); αβ (164 mg, 17% yield); ββ (25 mg, 2.5% yield).
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(*Received in USA* 14 *June* 1996; *revised* 1 *July* 1996; *accepted* 3 *July* 1996)