Pergamon

Tetrahedron Letters, Vol. 38, No. 31, pp. 5569-5572, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01246-X

Stereocontrol by Intrinsic Antiparallel Double Repulsion on Diacetone-D-Glucose Template. Diastereoselective Synthesis of 3(*S*)-Isothiocyanato-3-deoxy-3-C-vinyl glucose *via* (3,3)-Sigmatropic Rearrangement of Allylic Thiocyanates

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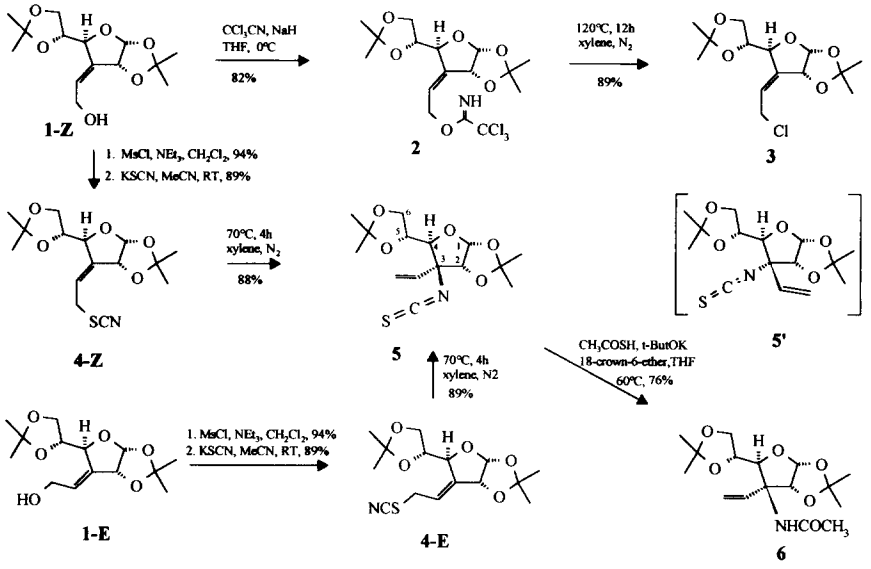
Abstract: A stereoselective synthesis of the branched-chain sugar 3(*S*)-isothiocyanato-3-deoxy-3-C-vinyl glucose *via* (3,3)-sigmatropic rearrangement of allylic thiocyanates prepared from D-glucose is presented. The side chain at C-4 of the substrates **4-Z**, **4-E** and **8-E** is not a decisive factor for stereocontrol in the (3,3)-sigmatropic rearrangement of allylic thiocyanates, and the 1,2-*O*-isopropylidene group in each isomer profoundly affects the direction of the rearrangement.

The (3,3)-sigmatropic rearrangement of allylic *trichloro*-acetimidates has been widely used for the stereoselective synthesis of amines[1] and branched-chain amino sugars[2]. In a previous report we presented a new synthetic route to diastereomerically pure 1,3-imidazolidin-2-thiones *via* a tandem of (3,3)-sigmatropic rearrangement of chiral thiocyanates followed by stereoselective intramolecular amine addition to the arising isothiocyanates[3]. Now we report an extension of this methodology to sugar allylic thiocyanates and illustrate its potential for stereocontrolled synthesis of the branched-chain sugar 3(*S*)-isothiocyanato-3-deoxy-3-C-vinyl glucose **5** as a suitable synthon for the synthesis e.g. myriocins[4a], mycestericins[4b] and branched-chain amino sugar nucleosides[5].

The substrates for the aza-Claisen rearrangements were 3-C-(hydroxymethyl)methylene derivatives of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranoses, **1-Z**[6] and **1-E**[6] (Scheme 1). The thermal Overman rearrangement of trichloroacetimidate **2** (xylene, 139°C, 6h), prepared from **1-Z** by the reaction of CCl_3CN/NaH in THF, unexpectedly led to the formation of allylic chloride **3** in 89% (Scheme 1). With the aim to examine similar methodology for introduction of nitrogen functionality into 3-position of glucose, we investigated the rearrangement of allylic thiocyanate **4-Z**. The starting thiocyanate **4-Z** was prepared by S_N2 displacement of *O*-mesyl group in corresponding mesylate, derived from allylic alcohol **1-Z**, by thiocyanate group (KSCN/CH_3CN) (Scheme 1). The thermal rearrangement of thiocyanate **4-Z** was carried out at 70°C in xylene under N_2 for 4h with high yield of crystalline isothiocyanate **5**, as the sole reaction product[7a] in 88% yield after silica-gel chromatography. The diastereoisomer **5'** was not detected in the reaction mixture. Although the stereochemistry of the quarternary carbon center (C-3) introduced in **5** was not established by its NMR spectral analysis, it was determined by the X-ray analysis as (*S*)[8]. Reaction of **5** with thioacetic acid[7b] (1.3 mol) and t-ButOK (0.2 mol) in the presence of 18-crown-6-ether in THF at 60°C (4h) gave 3(*S*)-acetylamino-3-deoxy-3-C-vinyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **6** in 76% yield.



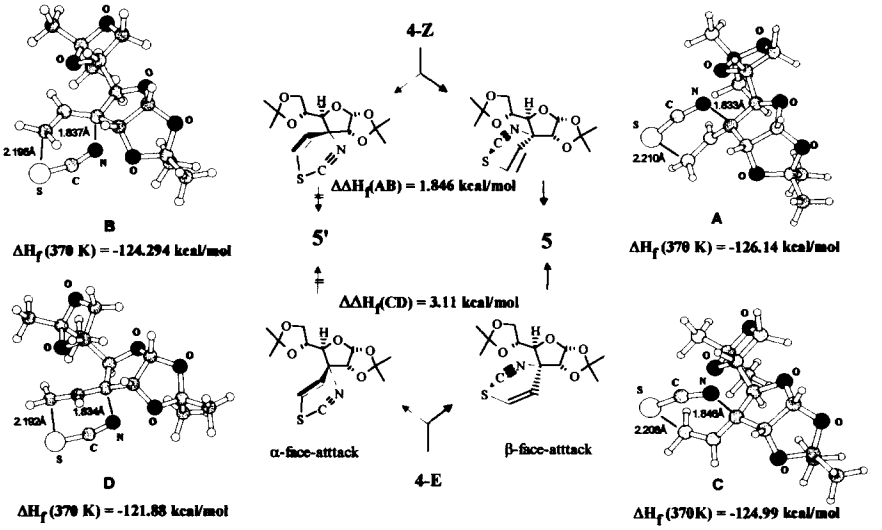
Scheme 1

A plausible basis for the exclusive formation of **5** from **4-Z** is illustrated in Scheme 2. By considering of the two transition states possible for (3,3)-sigmatropic rearrangement, it is apparent that the formation of the N-C bond from the α-face of the furanose ring suffers severe non-bonded interaction between the 1,2-isopropylidene group and the NCS part (in the case unfavorable transition state). Therefore, the N-C bond formation occured preferentially from the less hindered β-face of the furanose ring. The calculated transition structures[9] (AM1 method) for (3,3)-sigmatropic rearrangements **4-Z->5** (transition state **A** with ΔHf (370 K) = -126.14 kcal/mol, Scheme 2) and **4-Z->5'** (transition state **B** with ΔHf (370 K) = -124.294 kcal/mol, Scheme 2) are in agreement with our observations. The calculated energy difference is 1.846 kcal/mol in favour of transition state **A** and predicts the formation of diastereomer **5**.

Although the transition state argument mentioned above for the stereoselective outcome of the rearrangement seems to be reasonable, an assumption that the large substituent at C-4 in the furanose ring might participate in the stereoselectivity could not be excluded. To clarify this possibility, the rearrangement of thiocyanates **4-E** (Scheme 1) and **8-E** (Scheme 3), was next investigated. The substrate **4-E** was prepared in an analogous manner as **4-Z** and the rearrangement of **4-E** was studied under the same conditions as for **4-Z** (Scheme 1). In contrast to the nonselective Johnson-Claisen rearrangement of **1-E**[10], the rearrangement of **4-E** proceeded with the complete stereocontrol and product **5** was isolated as the sole product in 89% yield. The calculated energy difference[8] (AM1 method) between two possible transition states (**4-E->5**, transition state **C** with ΔHf (370 K) = -124.99 kcal/mol and **4-E->5'**, transition state **D** with ΔHf (370 K) = -121.88 kcal/mol, Scheme 2) is 3.11 kcal/mol and predicts exclusive formation product **5**. The thiocyanate **8-E** with a large 5,6-di-*O*-(*t*-butyldimethyl)silyl protecting groups was prepared from known[6] (*E*)-α,β-unsaturated ester **7** by a series of functional group manipulations: 1) selective removing 5,6-*O*-isopropylidene group with DDQ[11] (0.2 mol) in MeCN:H_2O=9:1 (87%), 2) 5,6-*O*-silylation of the resulting 5,6-diol with TBDMSCl/imidazole in DMF at 70°C (70%), 3) DIBAH reduction in THF (83 %), 4) mesylation of the resulting allylic alcohol with MsCl/NEt_3 in CH_2Cl_2 (90%), 5) displacement of *O*-mesyl group by thiocyanate group by KSCN in MeCN (89%), (Scheme 3).

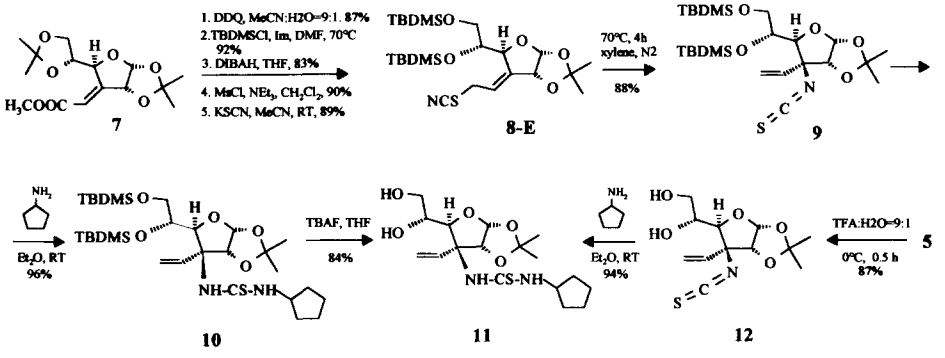
Finally, the aza-Claisen rearrangement of **8-E** was accomplished under the same conditions as for **4-Z** and **4-E** (70°C, xylene, N_2, 4h) and the isothiocyanate **9** was isolated as the sole product in 88% yield. The absolute configuration at C-3 in **9** was unambiguously determined by chemical transformations (Scheme 3). Thus, reaction of the

isothiocyanate **9** with cyclopentylamine led to thiourea **10** in 96% yield.



Scheme 2

Subsequent removing 5,6-*O*-silyl groups with TBAF in THF afforded unprotected thiourea **11** in 84%. This compound is in all respect identical with the unprotected thiourea **11** which was prepared from **5** as follows: Treatment of **5** with TFA/H_2O[12] (TFA:H_2O=9:1) afforded unprotected isothiocyanate **12** in 96% yield, which was converted to thiourea **11** in 94% yield after addition of cyclopentylamine. Surprisingly, the absolute configuration at C-3 in **9** is the same as in **5.**



Scheme 3

These facts led to the conclusion that the side chain at C-4 of the hexofuranosidic substrates **4-Z**, **4-E** and **8-E** is not a decisive factor for stereocontrol in the (3,3)-sigmatropic rearrangement of allylic thiocyanates, and that the 1,2-*O*-isopropylidene group in each isomer profoundly affects the direction of the rearrangement.

Acknowledgement : The present work was supported by Grant Agency (No. 1/3229/96) from the Ministry of Education, Slovak republic and Tempus Structural Joint European Project S-JEP-09101-95.

REFERENCES AND NOTES

1. Overman, L. E. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 579.
2. Dyong, I., Weigand, J., Merten, H., *Tetrahedron Lett.* **1981**, *22*, 2965. Fleet, G. W. J., Gough, M., J.,*Tetrahedron Lett.* **1982**,

23, 4509. Fleet, G. W. J., Gough, M. J., Shing, T. K. M., *Tetrahedron Lett.* **1983**, *24*, 3661. Gonzales, F. S., Berenguel, A. V., Mateo, F. H., Mendoza, P. G., Baer, H. H., *Carbohydrate Res.*, **1992**, *237*, 145. Fraser-Reid, B., Alonso, R. A., McDevitt, R. E., Rao, B., V., Vite, G. D., Zottola, M. A., *Bull. Soc. Chim.* B **1992**, *101*, 617.

3. Martinková, M., Gonda, J., *Tetrahedron Lett.* **1997**, *38*, 875.

4.a)Yoshikawa, M., Yokokawa, Y., Okuno, Y., Murakami, N., *Tetrahedron* **1995**, *22*, 6209. b) Fujita, T., Hamamichi, N., Matsuzaki, T., Kitao, Y., Kiuchi, M., Node, M., Hirose, R., *Tetrahedron Lett.* **1995**, *47*, 8599.

5. Hossain, N., Papchikhin, A., Plavec, J., Chattopadhyaya, J., *Tetrahedron* **1993**, *49*, 10133.

6. Tronchet, J. M., Gentile, B., *Carbohydr. Res.* **1975**, *44*, 23.

7.a) All compounds showed ^{1}H, ^{13}C, IR and HRMS spectra consistent with the reported structures. All new compounds gave satisfactory elemental analysis. A typical procedure for the preparation of **5**: A solution of the thiocyanate **4-Z** (**4-E**) (0.1g, 0.00305mol) in xylene (5 ml) was heated at 70°C for 3h under N_2. The solvent was then removed under vacuum. The crude product was chromatographed (20% ethyl acetate in hexane) and afforded 0.089g (89%) of **5** as a white crystals. **5**: m.p.= 81-83°C, IR($CHCl_3$): 2040 cm^{-1} (NCS). ^{1}H NMR data (300 MHz, $CDCl_3$): 1.33 (6H, s, $(CH_3)_2$), 1.39 (3H, s, CH_3), 1.55 (3H, s, CH_3), 4.08 (1H, dd, J=5.6, 8.8 Hz, H-6), 4.09 (1H, d, J=7.2 Hz, H-4), 4.12 (1H, dd, J=5.4, 8.8 Hz, H-6), 4.21 (1H, ddd, J=5.4, 5.6, 7.2 Hz, H-5), 4.52 (1H, d, J=3.5 Hz, H-2), 5.41 (1H, d, J=10.5 Hz, H-8cis), 5.60 (1H, d, J=17.0 Hz, H-8trans), 5.92 (1H, dd, J=10.5, 17.0 Hz, H-7), 5.94 (1H, d, J=3.5 Hz, H-1). ^{13}C NMR data (75.42 MHz, $CDCl_3$):25.3, 26.5($C(\underline{C}H_3)_2$), 26.7, 26.8 ($C(\underline{C}H_3)_2$), 66.6 (C-6), 73.4 (C-5), 75.1 (C-3), 82.4 (C-4), 88.2 (C-2), 104.4 (C-1), 109.6 ($\underline{C}(CH_3)_2$), 113.4 ($\underline{C}(CH_3)_2$), 118.2 ($\underline{C}H_2$=CH), 130.7 (CH_2=$\underline{C}$H). b) Drobnica, L., Kristian, P., Augustin, J. in: *The Chemistry of Cyanates and their Thio Derivatives* (Patai S., Ed.), p. 1122. Wiley, New York 1977. Schoepfer, J., Marquis, C., Pasquier, C., Neier, R., *J. Chem. Soc., Chem. Commun.* **1994**, *8*, 1001.

8. Single-crystal X-ray diffraction: **5**: Empirical formula $C_{15}H_{21}NO_5S$, m.w. 327.39, orthorhombic, space group $P2_12_12_1$ (No. 19), a=9.423(7), b=10.950(11), c=16.530(9) Å, V=1705.7(2) $Å^3$, Z=4, D_c=1.275cm^{-3}, F(000)=696. A colorless plate-like crystal of the dimensions 0.2x0.45x1.0 mm (from acetone/hexane) was measured at 293(2) K on CAD4 diffractometer with graphite-monochromated MoK_α radiation (λ=0.71073 Å). Absorption was neglected (μ=0.124mm^{-1}). The cell parameters were determined from 25 reflections in the 13-14° θ-range. The intensities variation of 3%. Of 3363 measured reflections, 3354 were unique (R_{int}=0.026) and 2932 were regarded as "observed" according to the $I \geq 2\delta(I)$ criterion. Data treatment: the structure was solved by direct methods (SHELX86) and refined by SHELXL93 using a full-matrix least-squares procedure based on F^2. Hydrogen atoms were refined isotropically, all other atoms anisotropically. Convergence for observed reflections and 283 parameters was achieved at R=0.0312, R_w=0.0831, GOF=1.040, $(\Delta/\sigma)_{max}$= ±0.001. The final difference electron density map was featureless with extremum values of 0.30; -0.16 e $Å^{-3}$.

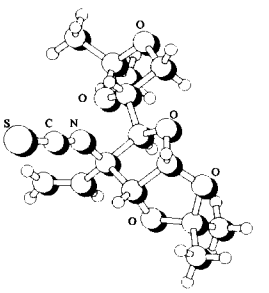


Figure The molecular structure of **5**.

9. Theoretical calculations were carried out at the semiempirical RHF AM1 method, as implemented in the MOPAC 6.0 program (Stewart, J. P. P. *J. Comput. Chem.* **1989**, *10*, 209; Stewart, J. P. P. *ibid.* **1988**, *44*, 5597; Stewart, J. P. P. *QCPE* **1989**, program 455). The transition states for intramolecular cyclization **4-Z->5/5'** (**A**, **B**) and **4-E->5/5'** (**C**, **D**) were located using the SADDLE routine implemented in MOPAC. Further refinements of these approximate transition state geometries were carried out by minimizing the norm of energy (Baker, J. *J. Comput. Chem.* **1986**, *7*, 385) using the eigenvector-following (EF) method. The resulting geometries have a one negative vibration frequency (McIver, J. W.; Komornicky, A. *J. Am. Chem. Soc.* **1972**, *94*, 2625) and verification using intrinsic reaction coordinate calculations for modes 1 and -1 leads to the reactants and products of the reactions.

10. Tadano, K., Idogaki, Y., Yammada, H., Suami, T., *Chem. Lett.* **1985**, 1925. Tadano, K., Idogaki, Y., Yammada, H., Suami, *J. Org. Chem.* **1987**, *52*, 1201.

11. Fernández, J. M. G., Mellet, C. O., Marín, A. M., Fuentes, J., *Carbohydr. Res.* **1995**, *274*, 263.

12. Fernández, J. M. G., Mellet, C. O., Blanco, J. L. J., Fuentes, J., *J. Org. Chem.* **1994**, 59, 5565.

(*Received in UK* 29 *April* 1997; *revised* 17 *June* 1997; *accepted* 20 *June* 1997)