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A Novel Reductive Fragmentation Reaction in Thio-Sugar Chemistry

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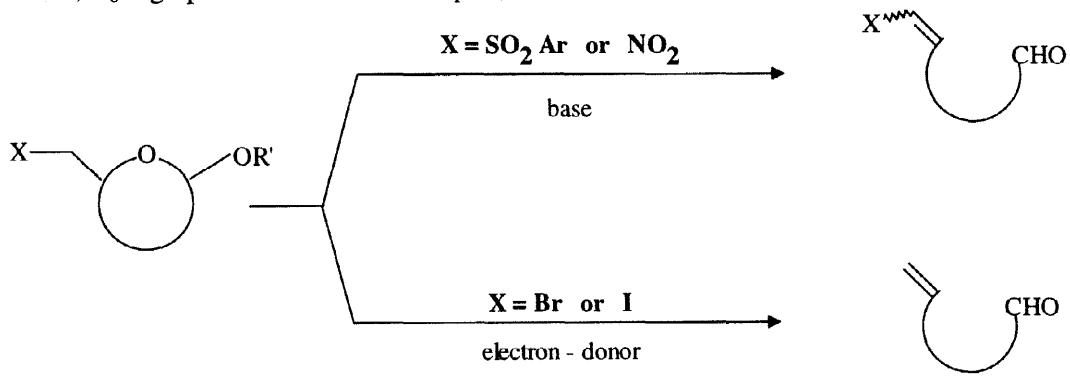
Abstract : When reacted with Grignard reagents, azaheterocycle/thiosugar hybrids such as the benzothiazo-2-yl derivative **1** undergo a novel type of sugar ring-cleavage to build up chiral polyoxygenated vinyl sulfides with a high degree of stereocontrol.

Key Words : thiosugars / Grignard reagents / ring-cleavage / vinyl sulfides

The interest for stereocontrolled synthesis of natural substances has urged many groups to develop novel pathways to chiral synthons starting from carbohydrates[1]. The stereocontrolled elaboration from sugars of chiral polyhydroxylated acyclic systems represents a major synthetic challenge with regard to the construction of chiral building blocks.

In this field, several methodologies dealing with ring-cleavage of glycosidic compounds have been developed. Base-induced fragmentations involving pyranosides activated at the primary position by an arylsulfonyl[2] or a nitro group[3] have been reported. On the other hand, reductive fragmentation methods based on the decyclization of halogen-activated furanoid or pyranoid systems were described using various electron-donors i.e. zinc[4], C_8K-graphite or zinc-silver couple[5], samarium diiodide[6] :



In the course of our current exploration of the chemistry of thio-sugars, we herein report an original fragmentation of aza-heterocycle / thio-sugar hybrids[7] leading - with a high degree of stereocontrol - to vinyl sulfides engrafted upon a stereochemically-defined polyoxygenated appendage.

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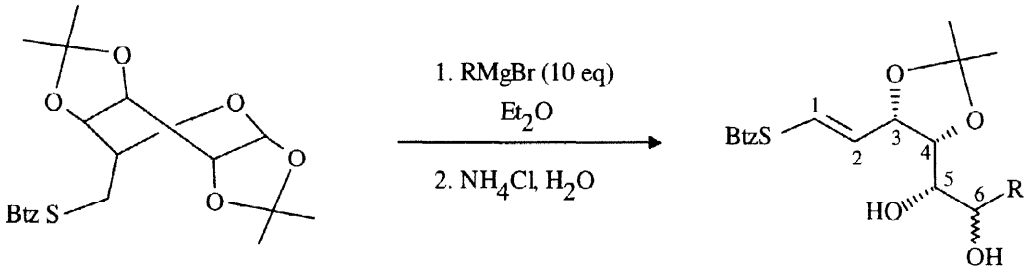
This new Grob-type[8] heterocyclic fragmentation process, based on a cooperative aza / thia-assistance[9], was first applied to the benzothiazol-2-yl (Btz) derivative **1**[7] using a range of traditional aliphatic Grignard reagents :

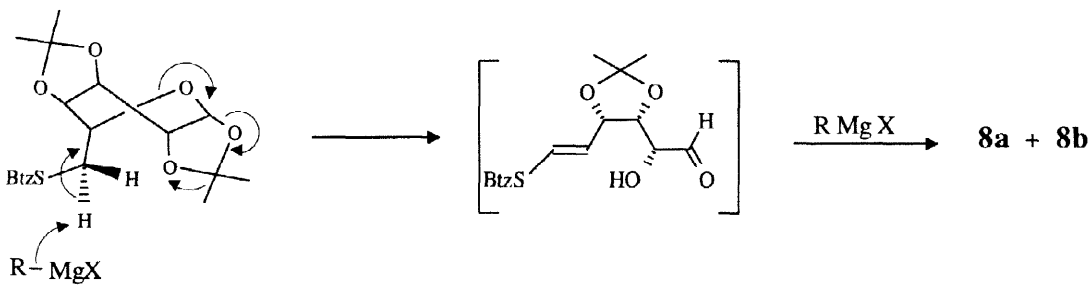


1 **8a** (6R) and **8b** (6S)

This new fragmentation reaction requires :

i/ the presence in the substrate of an heteroarylthio group which favours the formation of a carbanion in alpha position to the sulfur atom. The lack of reactivity of analogous 1,2:3,4-di-*O*-isopropylidene-6-*S*-phenyl-6-thio-D-galactopyranose under the same conditions is supporting this argument.

ii/ a basic Grignard reagent which acts both as proton-extruding agent and nucleophilic species as shown in the following scheme :



The yield and the stereoselectivity of this base-induced ring fragmentation are dependent on the nature of the Grignard reagent used. Table 1 depicts for RMgX the influence of the alkyl chain length and of the halogen atom involved.

R	Et	Pr	n-Bu	s-Bu	n-pentyl	Et	Pr	iPr	Bu
X	Br	Br	Br	Br	Br	I	I	Cl	I
Yield	80	80	71	79	44	42	50	80	33
6R / 6S	3 : 2	2 : 1	9 : 1	9 : 1	9 : 1	9 : 1	9 : 1	9 : 1	9 : 1

Table 1 : Influence of the Grignard reagent on the fragmentation's outcome

The analysis of the above results shows that the fragmentation yields are in agreement with the known relative basicities of the organomagnesium reagents. Trials involving less basic phenyl, benzyl or allyl reagents remained unsuccessful. As expected for similar reasons, the bromo (and chloro) Grignard reagents gave far better results than the corresponding iodo compounds.

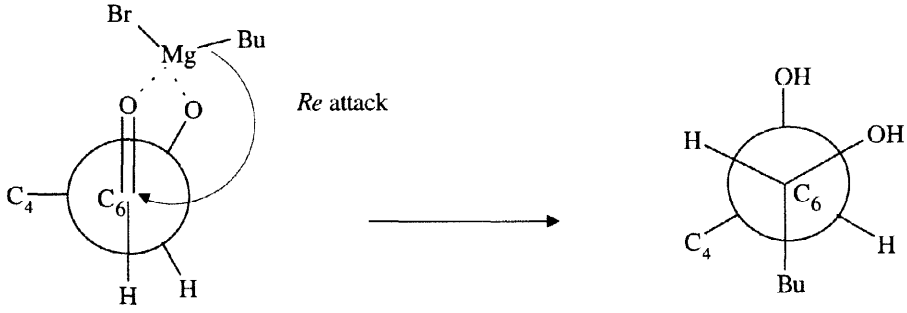
Moreover, the diastereofacial selectivity of the terminal nucleophilic attack on C-6 is shown to be related to the bulkiness of the alkyl group involved.

The most attractive features of this original reaction are :

i/ the exclusive formation of (E)-configurated vinyl sulfides (as proven by the value of the $J_{5,6}$ coupling constant[10])

ii/ the good diastereoisomeric excess attained when adequate basic Grignard reagents are selected.

The stereoselectivity in favour of the (5S, 6R) epimer as compared to the (5S, 6S) epimer could be foreseen by the chelating Cram's model[11] applied to the supposed transient α-hydroxyaldehyde intermediate. The *Re*-attack should be favoured, as depicted below :



5S, 6R major epimer

Assigning the respective configuration of both epimers could not been brought through an X-ray crystal analysis. Each epimer was therefore submitted independently to a degradation sequence involving i) vinyl sulfide ozonolysis ii) acetonide hydrolysis iii) acetylation : the pyrano derivatives thus obtained from the major epimer **8a** and the minor epimer **8b** were shown by NMR to be related to the D-gulo and the L-manno series, respectively. This configuration correlation fully supported the hypothesis suggested by the Cram's model.

Following the study of the fragmentation of benzothiazol-2-yl derivative **1**, extension to the case of analogous thio-sugar / aza-heterocycle hybrids[7] was performed using n-butylmagnesium bromide as a standard reagent. The results presented in Table 2 show (with the exception of entries **3** and **7**) the general character of this fragmentation process with regard to yields and diastereoisomeric excesses :

hybrid	**nature of the heterocyclic moiety**	**yield (%)of vinyl sulfide**	**stereoselectivity 6R / 6S**
1	benzothiazol-2-yl	70	9 : 1
2	2-pyridyl	60	8,5 : 1,5
3	2-pyrimidyl	-	-
4	thiazolin-2-yl	70	8,5 : 1,5
5	1-methylimidazol-2-yl	50	8 : 2
6	benzoxazol-2-yl	60	9,5 : 0,5
7	5-phenyltetrazol-2-yl	11	n.d.

Table 2 : Fragmentation of heterocyclic congeners of **1**

In summary, we have described an original and highly diastereoselective reductive fragmentation which gives access to vinyl sulfides bearing a chiral polyhydroxylated appendage. Such compounds offer various possibilities of activation : their use in stereocontrolled synthesis has permitted to develop new and original pathways[12] to oxa-[13] and azacycles[14] of biological interest. Further extension of this methodology to miscellaneous series of sugars is under current study in this laboratory and will be reported in due course.

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10. Fully satisfactory spectroscopic (IR and 300 MHz ^{1}H NMR) were obtained for all new compounds. **8a** crystalline solid, mp = 121 °C (from Et_2O), $[\alpha]_D$ + 47 (*c* 0.5 , $CHCl_3$) ; ^{1}H-NMR data ($CDCl_3$) : 0.88 (t, 3H, CH_3(Bu), 1.42 and 1.58 (s, 6H, $2CH_3$), 2.65 (d, 1H, J_{OH-6} = 4.5, OH-6), 2.80 (d, 1H, J_{OH-5} = 6.9, OH-5,), 3.51 (dd, 1H, H-5), 3.67 (m, 1H, H-6), 4.35 (dd, 1H, $J_{4,5}$ = 3.5, H-4), 4.87 (t, 1H, $J_{3,4}$ = 6.7, H-3), 6.37 (dd, 1H, $J_{2,3}$ = 7.9, H-2), 7.06 (d, 1H, $J_{1,2}$ = 15.8 ; H-1), 7.32 (t, 1H, H-6 Btz), 7.44 (t, 1H, H-5 Btz), 7.78 (d, 1H, $J_{6,7}$ = 7.9, H-7 Btz), 7.91 (d, 1H, $J_{4,5}$ = 7.9, H-4 Btz), ^{13}C-NMR data : 13.12 (CH_3(Bu)), 26.97 et 32.39 (CH_3(iPrd)), 70.01 (C-5), 71.65 (C-6), 77.15 (C-3), 78.37 (C-4), 120.18 (C-7 Btz), 120.96 (C-4 Btz), 123.77 (C-1 and C-6 Btz), 125.45 (C-5 Btz), 131.90 (C-2), 134.31 (C-7a Btz), 152.24 (C-3a Btz), 163.89 (C-2 Btz).
8b syrup, $[\alpha]_D$ + 64 (*c* 1.0, $CHCl_3$), ^{1}H-NMR data ($CDCl_3$) : ^{1}H-NMR data ($CDCl_3$) : 0.90 (t, 3H, CH_3(Bu), 1.44 and 1.56 (s, 6H, $2CH_3$), 1.74 (bd, 1H, OH-6), 2.35 (bd, 1H, OH-5), 3.49 (m, 1H, H-5), 3.62 (m, 1H, H-6), 4.51 (dd, 1H, $J_{4,5}$ = 2.8, H-4), 4.89 (t, 1H, $J_{3,4}$ = 7.4, H-3), 6.43 (dd, 1H, $J_{2,3}$ = 7.9, H-2,), 7.00 (d, 1H, $J_{1,2}$ = 15.0, H-1), 7.32 (t, 1H, H-6 Btz), 7.44 (t, 1H, H-5 Btz), 7.78 (d, 1H, $J_{6,7}$ = 7.9, H-7 Btz), 7.91 (d, 1H, $J_{4,5}$ = 7.9, H-4 Btz)
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