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Tetrahedron Letters 46 (2005) 5265–5268

Tetrahedron Letters

Fragmentation of carbohydrate anomeric alkoxyl radicals. Synthesis of highly functionalized chiral vinyl sulfones

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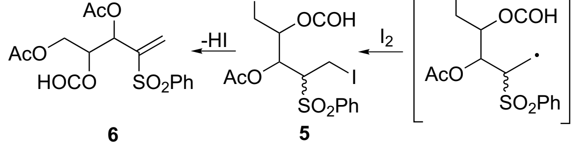
Received 20 May 2005; revised 9 June 2005; accepted 10 June 2005

Abstract—The reaction of derivatives of 3-acetyl-D-glucal, 3-acetyl-L-rhamnal, 3-acetyl-D-galactal, and 3-acetyl-D-lactal with sodium benzenesulfinate in acid medium catalyzed by $HgSO_4$ afforded diastereoisomeric mixtures of the corresponding 2,3-dideoxy-3-(phenylsulfonyl)-hexopyranoses through a Ferrier rearrangement. The anomeric alkoxyl radical fragmentation of these γ-hydroxy sulfones using the system (diacetoxyiodo)benzene and iodine gave vinyl sulfones with structures of 1,2-dideoxy-4-*O*-formyl-2-(phenylsulfonyl)-pent-1-enitol and configurations D-*erythro*, L-*erythro*, and D-*threo* at the two stereogenic centers.

Vinyl sulfones are extremely useful as Michael acceptors and 2π partners in cycloaddition and cross-metathesis reactions.[1] Many methods for preparing vinyl sulfones have been developed. Among these the ionic and radical addition of sulfonate derivatives to alkenes and alkynes is one of the most important.[2] Furthermore, the stability and ease of further transformation of the sulfonyl group via elimination by either reductive or alkylative desulfonylation confers further advantages to vinyl sulfones as versatile synthetic intermediates.[3]

During the past years we have carried out a systematic effort aimed at investigating the reaction of carbohydrate anomeric alcohols with hypervalent iodine reagents in the presence of iodine. The influence of the electronic factors in the promoted alkoxyl radical fragmentation (ARF) reaction has been studied by analyzing the C-2 substituent effect in detail.[4]

On the other hand, the rearrangement of 3-acetylated glycals (**1**) with aqueous sulfuric acid and catalytic amounts of mercury(II) sulfate is an appropriate procedure for the synthesis of *E*-enals such as **2** (Scheme 1).[5] These unsaturated aldehydes readily undergo in situ direct Michael 1,4-addition with nucleophilic species ($Z = N_3$ or PhS) to give 2,3-dideoxy-hexopyranoses (**3**).[6]



Scheme 1. ZH = N_3H, PhSH, $PhSO_2H$. ARF = alkoxyl radical fragmentation.

With these results in mind, we were particularly interested in synthesizing the hitherto unknown 2,3-dideoxy-3-(phenylsulfonyl)-hexopyranoses (**4**) by using sodium benzenesulfinate as nucleophile in the Michael addition. The 1,3-hydroxysulfones can be subsequently transformed into β-iodosulfones (**5**) by using our ARF methodology and hence to vinyl sulfones (**6**). The chiral

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Keywords: Radical reaction; Alkoxyl radical; Carbohydrate; Vinyl sulfone.

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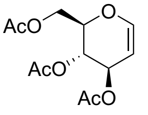
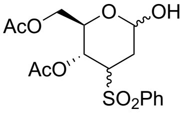
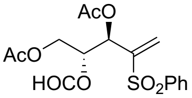
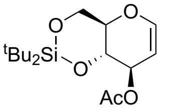
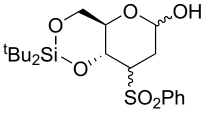
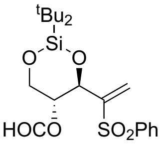
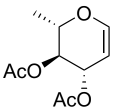
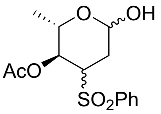
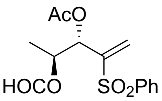
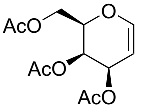
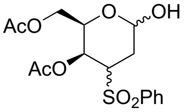
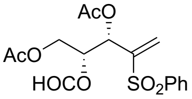
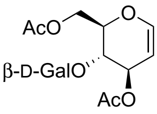
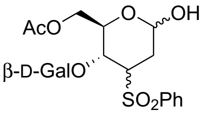
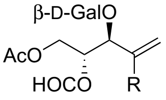
doi:10.1016/j.tetlet.2005.06.043

Table 1. Synthesis of vinyl sulfones

Entry	Glycal	Time, t_1/t_2 (h)	γ-Hydroxy sulfone[a]	Time, t_3/t_4 (h)	Vinyl sulfone[b]	Yield[c] (%)
1	 **7**	1.5/1.5	 **12**	1/0.75	 **17**	43
2	 **8**	23/3	 **13**	1/21[d]	 **18**	50
3	 **9**	1/1	 **14**	0.5/0.75	 **19**	44
4	 **10**	1/1	 **15**	1/0.3	 **20**	43
5	 **11**	1/15	 **16**	1/25[e]	 **21** R = SO_2Ph **22** R = H	**21** (40) **22** (8)

[a] Reagents and conditions for mmol of substrate: $HgSO_4$ (0.045 mmol), H_2SO_4 (5 mM, 27 mmol), 1,4-dioxane (1.3 mL), reflux, t_1, then $NaSO_2Ph$ (10 mmol), AcOH (1.3 mL), reflux, t_2.

[b] Reagents and conditions for mmol of substrate: (diacetoxyiodo)benzene (1.3 mmol), I_2 (0.9 mmol), CH_2Cl_2, rt, under irradiation with a 80 W tungsten-filament lamp, t_3, then Et_3N (5 mmol), rt, t_4.

[c] Overall yield from the corresponding 1,5-anhydro-2-deoxy-hex-1-enitol (glycal).

[d] DBU (3 mmol) was used in the dehydroiodination reaction.

[e] Py (20 mmol) was used in the dehydroiodination reaction.

1,2-dideoxy-2-(phenylsulfonyl)-pent-1-enitol derivatives thus formed may be potentially useful building blocks in organic synthesis.

The 2,3-dideoxy-3-(phenylsulfonyl)-hexopyranoses outlined in Table 1 **12**–**16** were prepared from the corresponding 1,5-anhydro-2-deoxy-hex-1-enitol (glycal)[7] **7**–**11** by adaptation of a procedure[6a] for the synthesis of 3-azido-2,3-dideoxy-hexopyranoses. A solution of the glycal in aqueous 1,4-dioxane containing $HgSO_4$ and H_2SO_4 was refluxed for a specific period of time (see, Table 1, t_1). Then sodium benzenesulfinate in acetic acid was added and the reaction mixture stirred at this temperature for the time specified in Table 1 (t_2).[8] As detected spectroscopically, the 1,3-hydroxysulfones were diastereoisomeric mixtures and the complexities of the spectra precluded a comprehensive assignment of all proton and carbon resonances. Notwithstanding, some structural features such as the disappearance of the double bond or the presence of the two hydrogens at C-2 and the aromatic ring can be easily inferred. In this case, as precursor of a non-stereogenic center, the C3 stereocontrol is irrelevant and no diastereoisomeric analyses were attempted at this stage. It is worth noting that the sensitive di-*tert*-butylsilanediyl protective group and the glycosidic linkage survived the acidic reaction conditions (entries 2 and 5, respectively). Crude homogeneous hydroxysulfones, which gave correct elemental analysis were used without purification in the fragmentation reaction.

The ARF reactions were performed under the conditions stated in Table 1, with (diacetoxyiodo)benzene (DIB) and iodine in CH_2Cl_2 at room temperature and irradiation with two 80 W tungsten filament lamps. Complete consumption of the starting material was observed in all cases.[9]

At the beginning of the ARF reaction, a transient less polar compound, presumably the β-iodo sulfone, was observed by TLC. This intermediate was afterward, during the work-up and the chromatographic purification steps, almost completely transformed into the vinyl sulfone. From a practical point of view the dehydroiodination reaction was better accomplished by directly adding an excess of base, TEA, DBU, or Py to the reaction mixture at the end of the ARF. Using this methodology 1,2-dideoxy-2-(phenylsulfonyl)-pent-1-enitol derivatives possessing two stereogenic centers with D-*erythro* (**17**, **18**, and **21**), L-*erythro* (**19**), and D-*threo* stereochemistries (**20**) were obtained. The reactions were relatively clean and the products were easily purified by chromatography, although diastereoisomeric mixtures of crude hydroxy sulfones were used. Besides vinyl sulfone **21**, a small amount of desulfonylated compound **22** was observed in the ARF of the disaccharide **16** (entry 5). The desulfonylation may occur by β-fragmentation of the C-2 radical intermediate. The structures of the vinyl sulfones were determined by extensive NMR studies including COSY, DEPT, HMBC, and HMQC experiments allowing the unequivocal assignment of all carbon and hydrogen resonances.

Although the overall yield of the vinyl sulfones from the starting glycals was modest (40–50%), it is nonetheless striking taking into account the number of chemical transformations involved. The overall yield is indeed very similar to that obtained in the three-step synthesis of vinyl azides also using an ARF methodology.[4e]

On the other hand, the easy accessibility of the starting glycals, the operational simplicity of this two-step methodology and the possible further synthetic transformations of the vinyl sulfones are noteworthy and justify exploitation of these substances as chiral synthons. These facts together with the richness of the sugar chemistry available, allow prior structural modifications and protection patterns of the carbohydrate that will increase the potential of the method.

Acknowledgments

This work was supported by the Investigation Programs nos. CTQ2004-06381/BQU and CTQ2004-02367/BQU of the Ministerio de Educación y Ciencia, Spain, cofinanced with the Fondo Europeo de Desarrollo Regional (FEDER). C.R.A. thanks the Program I3P-CSIC for a fellowship.

Supplementary data

Experimental procedure and characterization data for compounds **12**–**22** are provided. Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.06.043.

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7. The tri-*O*-acetyl-D-glucal (**7**), precursor of sulfones **12** and **13**, is commercially available. Tri-*O*-acetyl-L-rhamnal (**9**), tri-*O*-acetyl-D-galactal (**10**), and tri-*O*-acetyl-D-lactal (**11**) were easily prepared according to: Shull, B. K.; Wu, Z.; Koreeda, M. *J. Carbohydr. Chem.* **1996**, *15*, 955–964.
8. General procedure for the synthesis of 2,3-dideoxy-3-(phenylsulfonyl)-aldoses (**12**–**16**). A solution of the

corresponding 2-deoxy-hex-1-enitol (1 mmol) in 1,4-dioxane (1.3 mL) containing $HgSO_4$ (0.045 mmol) and aqueous H_2SO_4 (5 mM, 5.4 mL) was stirred at reflux temperature for a specified period of time (Table 1). Then $NaSO_2Ph$ (10 mmol) and AcOH glacial (1.3 mL) were added and the stirring continued at this temperature for the time specified in Table 1. The reaction mixture was then poured into water and extracted with EtOAc. The organic layer was dried over Na_2SO_4, concentrated under vacuum, and the residue used in the next reaction without purification.

9. General procedure for the synthesis of vinyl sulfone compounds (**17**–**21**). A solution of the crude 3-(phenylsulfonyl)-2,3-dideoxy compounds obtained as described above in CH_2Cl_2 (20 mL) containing (diacetoxyiodo)benzene (1.3 mmol) and iodine (0.9 mmol) was stirred at rt, under irradiation with an 80 W tungsten-filament lamp for a specified period of time (Table 1). Et_3N (5 mmol) was added and the stirring was continued at this temperature for the time specified in Table 1. The reaction mixture was then poured into water and extracted with CH_2Cl_2. The organic layer was washed with 10% aqueous sodium thiosulfate, dried, and concentrated in vacuo. Chromatotron chromatography of the residue (hexanes–EtOAc mixtures) afforded the required vinyl sulfones.