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# Zinc-Mediated Fragmentation of Methyl 6-Deoxy-6-iodo-hexopyranosides

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**Summary.** An improved procedure was developed for the zinc-mediated fragmentation of protected and unprotected methyl 6-deoxy-6-iodo-hexopyranosides. The method employs sonication of the iodoglycoside with zinc dust in a *THF*/$H_2O$ mixture.

**Keywords.** Fragmentation; Glycosides; Halogens; Sonication; Zinc.

## Introduction

The zinc-mediated reductive fragmentation of methyl 6-deoxy-6-halo-hexopyranosides has been described for the first time by *Bernet* and *Vasella* in 1979 [1]. The 5,6-dideoxy-hex-5-enoses thus generated are useful chiral synthons and have found many applications in carbohydrate chemistry. Most notable is the synthesis of five-membered carbocycles by 1,3-dipolar cycloadditions [1,2] or radical cyclizations [3]. In addition, the fragmentation has also been used for the synthesis of azasugars [4] and complex natural products [5]. The corresponding methyl 5-deoxy-5-halo-pentofuranosides also undergo this fragmentation [6].

However, in spite of the many applications, the reductive fragmentation of $\omega$-haloglycosides continues to cause significant experimental difficulties. The original procedure calls for reflux with acid-washed zinc powder in aqueous alcohols [1]. This is still the most widely used protocol, but the yields are often moderate due to the instability of 5,6-dideoxy-hex-5-enoses at reflux and the formation of several byproducts including methyl 6-deoxy-hexopyranosides (C-6 reduction), 2,5,6-trideoxy-hex-5-enoses (C-2 deoxygenation), and 5,6-dideoxy-hex-5-enose dialkyl acetals (acetal formation) [1,3]. Recently, the addition of vitamin $B_{12}$ has been shown to give some improvement, allowing the fragmentation to be carried out at room temperature [7]. Using a better leaving group at the anomeric center, like the *p*-methoxyphenyl group, also gives higher yields [8], but this is not a convenient method for general use. Another procedure for the fragmentation employs the more reactive zinc-silver graphite in *THF* at room temperature [9]. Yields are here generally higher, and less byproducts are formed than when refluxing with zinc powder in aqueous alcohols.

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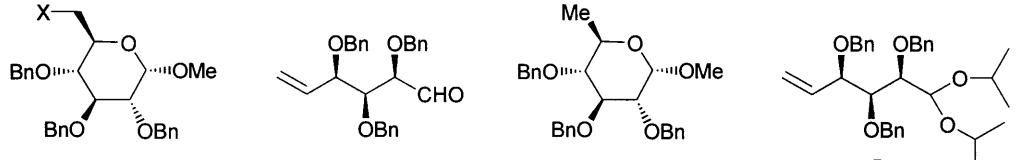
We have recently developed a domino reaction where methyl $\omega$-haloglycosides are fragmented with zinc and the resulting aldehydes are subsequently alkylated in a *Barbier* reaction [10]. Zinc serves a dual function in this reaction. First, it mediates the fragmentation of the haloglycoside; secondly, it activates an alkyl halide for the *Barbier* alkylation. During this work we had to find an efficient and high-yielding protocol for the fragmentation of methyl $\omega$-haloglycosides. Herein, we report a full account on these studies which resulted in the development of an improved fragmentation procedure.

## Results and Discussion

We first studied the fragmentation with benzyl-protected methyl glucopyranosides **1** and **2** (Scheme 1). Refluxing bromide **1** with acid-washed zinc powder in aqueous 2-propanol gave enal **3** in about 65% yield in accordance with previous observations [1]. The major byproducts formed were 6-deoxy glucoside **4** together with a small amount of acetal **5**. In order to avoid these byproducts, more reactive forms of zinc were investigated. Unfortunately, bromide **1** and iodide **2** did not react with *Rieke* zinc, zinc graphite, or zinc-silver graphite in *THF* at room temperature or at reflux. Presumably, this lack of reactivity is due to the steric bulk of **1** and **2**, as sterically demanding protecting groups have previously been shown to inhibit the fragmentation [9].

Addition of an alcohol has been shown to enhance the rate of the fragmentation with these reactive forms of zinc [9b]. Indeed, treatment of iodide **2** with *Rieke* zinc in a *THF*/methanol mixture at reflux afforded complete fragmentation. Unfortunately, the product **3** had epimerized at C-2, maybe due to traces of potassium in the *Rieke* zinc. In order to avoid possible epimerizations, acetic acid was then added instead of methanol. However, this led to reduction of the iodide to afford deoxyglycoside **4**. Virtually complete reduction to **4** was also observed upon refluxing **2** with zinc powder and acetic acid in aqueous 2-propanol. Bromide **1** gave similar results; however, it is less reactive than iodide **2**, and the latter was therefore chosen for general use.

As it appeared important to have an alcohol and/or an acid present during the fragmentation, several experiments were then conducted with a *Lewis* acid. Treatment of **2** with *Rieke* zinc and *TMS*Cl in *THF*/2-propanol caused almost complete conversion to acetal **5**. Interestingly, no reduction of the iodide was observed under these conditions. To prevent acetal formation the reaction was repeated without 2-propanol. Gratifyingly, this now gave very clean formation of the desired enal **3**. The fragmentation was most conveniently carried out with zinc

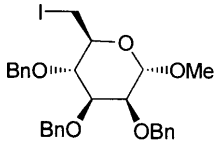
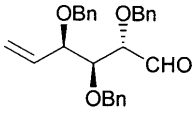
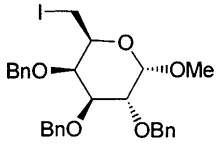
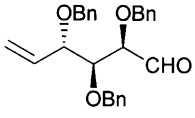
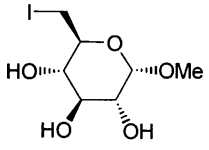
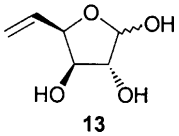
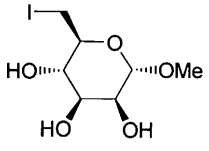
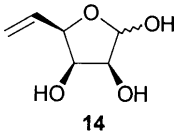
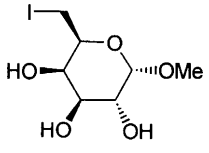
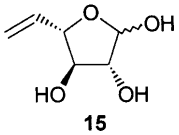



**1**: *X* = Br
**2**: *X* = I

**3** **4** **5**

**Scheme 1**

**Table 1.** Zinc-mediated fragmentation of methyl 6-deoxy-6-iodo-hexopyranosides; conditions: A: Zn, *TMS*Cl, *THF*, sonication, 40°C, 4–6 h; B: Zn, *THF*:$H_2O$ = 9:1, sonication, 40°C, 1 h; C: Zn, *THF*:$H_2O$ = 4:1, sonication, 40°C, 1 h

| Entry | Iodoglycoside | Conditions | Product | Yield/% |
|---|---|---|---|---|
| 1 | **2** | A | **3** | 85 |
| 2 | **2** | B | **3** | 94 |
| 3 |  **6** | A |  **11** | 86 |
| 4 | | B | | 89 |
| 5 |  **7** | A |  **12** | 85 |
| 6 | | B | | 93 |
| 7 |  **8** | C |  **13** | 94 |
| 8 |  **9** | C |  **14** | 94 |
| 9 |  **10** | C |  **15** | 95 |

powder, as *Rieke* zinc did not provide better results and is more tedious to prepare. Refluxing **2** with zinc powder and *TMS*Cl worked well when starting with less than 1 g of **2**. On larger scale, however, the reaction proved less efficient, presumably due to precipitation of zinc salts onto the metallic zinc surface. Therefore, more reproducible conditions were sought and sonication was investigated. To the best of our knowledge this fragmentation has never been achieved under sonication conditions prior to our first report in 1999 [10a]. It turned out that sonication at 40°C caused clean and reproducible conversion into enal **3** (Table 1, entry 1). Even on a 10 g scale this procedure proved very reliable. A more finely grinded zinc (<10 μm) was used for these sonication experiments. Under reflux conditions this type of zinc was less efficient due to aggregation, and a more coarse powder was

used for these experiments. The general applicability of the sonication protocol is further illustrated by the fragmentation of protected mannoside **6** and galactoside **7** (Table 1, entries 3 and 5).

Good yields were obtained under these conditions, but it still bothered us that some material was always lost. This was presumably due to slight decomposition of the enals **3**, **11**, and **12**, as no other products were isolated from these reactions. The problem seemed to be the acidic conditions and the 4–6 h of reaction time. *TMS*Cl was therefore replaced by $H_2O$ hoping that a continuous wash of the zinc surface during the reaction would improve the reactivity. This turned out to work very well. The fragmentation was finished in less than 1 h giving slightly better yields of enals **3**, **11**, and **12** (Table 1, entries 2, 4, and 6).

The fragmentation in a *THF*/$H_2O$ mixture also proved well suited for unprotected iodoglycosides **8**–**10** giving rise to furanoses **13**–**15** (Table 1, entries 7–9). The very high yields of all six fragmentation products **3** and **11**–**15** are noteworthy and constitute a testament to the efficiency of these reaction conditions. When unprotected iodoglucoside **8** was fragmented in anhydrous *THF* containing *TMS*Cl the product was not furanose **13**, but instead the corresponding methyl furanoside of **13** was formed. Apparently, a *Fischer* glycosylation with the liberated methanol takes place under these conditions.

Zinc appears to be the metal of choice for the reductive fragmentation of $\omega$-haloglycosides. Magnesium has been shown to give *Wurtz*-type homocoupling, presumably by a radical mechanism [11]. In our previously developed domino reaction we were able to replace zinc with indium [10b]. However, indium is a less reactive metal. In fact, when we sonicated unprotected glucoside **8** with indium in a *THF*/$H_2O$ mixture only a sluggish reaction was observed. Adding *TMS*Cl to the mixture gave full conversion of **8** in 12 h to give furanose **13** in 93% yield. Protected glucoside **2** could not be fragmented with indium, and only decomposition was observed on prolonged treatment. No fragmentation was also the result when **8** was sonicated with tin, antimony, or bismuth.

In conclusion, we have developed an improved procedure for the zinc-mediated fragmentation of methyl $\omega$-iodoglycosides. The fragmentation is most efficiently carried out with zinc dust under sonication in a *THF*/$H_2O$ mixture. For protected iodoglycosides a procedure under anhydrous conditions has also been developed employing *TMS*Cl. The latter method is useful when further synthetic transformations do not allow for the presence of $H_2O$ [10b].

## Experimental

Zinc was activated and dried immediately before use [10b]. Zinc powder (Fluka 96453) was used for fragmentations at reflux, whereas zinc dust (Aldrich 20.998-8) was used under sonication. All sonications were performed in a Branson 1210 ultrasonic bath. Thin-layer chromatography (TLC) was performed on aluminum plates precoated with silica gel (Merck 1.05554). Compounds were visualized by heating after dipping in a solution of 2.5 g $Ce(SO_4)_2$ and 6.25 g $(NH_4)_6Mo_7O_{24}$ in 250 $cm^3$ 10% aqueous $H_2SO_4$. Flash chromatography was performed using silica gel 60. Reverse phase flash chromatography was carried out with silica gel 60-50 $C_{18}$ (Macherey-Nagel). NMR spectra were recorded on a Varian Unity Inova 500 spectrometer. Microanalyses were conducted by the Department of Chemistry at the University of Copenhagen (data were in accordance with calculated values).

*General procedure for the fragmentation of benzyl protected iodoglycosides (conditions A and B)*

To a solution of 500 mg (0.87 mmol) methyl 2,3,4-tri-O-benzyl-6-deoxy-6-iodo-$\alpha$-*D*-glycopyranoside in 20 $cm^3$ *THF*, 569 mg (8.7 mmol) pre-activated zinc and 0.11 $cm^3$ (0.87 mmol) *TMS*Cl (condition A) or 2.2 $cm^3$ $H_2O$ (condition B) were added. The resulting suspension was sonicated at 40°C until TLC showed full conversion (A: 4–6 h, B: 1 h). Then, 30 $cm^3$ diethyl ether and 10 $cm^3$ $H_2O$ were added. The resulting biphasic system was filtered, and the layers were separated. The organic phase was washed with 10 $cm^3$ $H_2O$, 10 $cm^3$ brine, dried ($K_2CO_3$), filtered, and concentrated to give a bright yellow syrup which was purified by flash chromatography (hexane:ethyl acetate = 5:1).

*2,3,4-Tri-O-benzyl-5,6-dideoxy-D-xylo-hex-5-enose* (**3**; $C_{27}H_{28}O_4$)

Colorless syrup; spectroscopic data in accordance with literature [7].

*2,3,4-Tri-O-benzyl-5,6-dideoxy-D-lyxo-hex-5-enose* (**11**; $C_{27}H_{28}O_4$)

Colorless syrup; spectroscopic data in accordance with literature [7].

*2,3,4-Tri-O-benzyl-5,6-dideoxy-L-arabino-hex-5-enose* (**12**; $C_{27}H_{28}O_4$)

Colorless syrup; $R_f = 0.45$ (hexane:ethyl acetate = 5:1); $^1$H NMR ($CDCl_3$, 500 MHz): $\delta = 9.62$ (d, $J = 1.7$ Hz, 1 H), 7.40–7.20 (m, 15H), 5.90 (ddd, $J = 17.5$, 10.2, 7.7 Hz, 1 H), 5.44 (dd, $J = 17.5$, 1.7 Hz, 1 H), 5.42 (dd, $J = 10.2$, 1.7 Hz, 1 H), 4.65 (d, $J = 12.0$ Hz, 1 H), 4.61 (d, $J = 11.1$ Hz, 1 H), 4.56 (d, $J = 11.5$ Hz, 1 H), 4.55 (d, $J = 11.5$ Hz, 1 H), 4.50 (d, $J = 11.1$ Hz, 1 H), 4.20 (d, $J = 11.5$ Hz, 1 H), 4.11–4.08 (m, 2H), 3.89 (dd, $J = 7.7$, 3.8 Hz, 1 H) ppm; $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta = 202.43$, 137.84, 137.50, 137.18, 135.47, 128.35, 128.23, 128.16, 128.07, 127.96, 127.73, 127.70, 127.52, 120.16, 83.92, 81.20, 79.23, 74.24, 73.39, 70.06 ppm.

*General procedure for fragmentation of unprotected iodoglycosides (condition C)*

To a solution of 200 mg (0.66 mmol) methyl 6-deoxy-6-iodo-$\alpha$-*D*-glycopyranoside in 12 $cm^3$ *THF* and 3 $cm^3$ $H_2O$, 430 mg (6.6 mmol) pre-activated zinc were added, and the resulting suspension was sonicated at 40°C for 1 h. The reaction mixture was then filtered and concentrated to approximately 5 $cm^3$. The resulting solution was purified by reverse phase flash chromatography eluting with $H_2O$.

*5,6-Dideoxy-D-xylo-hex-5-enofuranose* (**13**; $C_6H_{10}O_4$)

Colorless syrup; $R_f = 0.21$ ($CHCl_3$:MeOH = 9:1); spectroscopic data in accordance with literature [12].

*5,6-Dideoxy-D-lyxo-hex-5-enofuranose* (**14**; $C_6H_{10}O_4$)

Colorless syrup; $R_f = 0.24$ ($CHCl_3$:MeOH = 9:1); 4:1 mixture of $\alpha$:$\beta$ anomers; $^1$H NMR ($D_2O$, 500 MHz): $\alpha$-anomer: $\delta = 5.86$ (ddd, $J = 17.5$, 10.5, 7.0 Hz, 1 H), 5.37–5.29 (m, 2H), 5.25 (d, $J = 4.5$ Hz, 1 H), 4.19–4.13 (m, 2H), 4.09 (t, $J = 4.5$ Hz, 1 H) ppm; $\beta$-anomer: $\delta = 5.23$ (d, $J = 5.0$ Hz, 1 H) ppm; $^{13}$C NMR ($D_2O$, 125 MHz): $\alpha$-anomer: $\delta = 133.32$, 120.18, 101.34, 82.03, 78.25, 73.50 ppm, $\beta$-anomer: $\delta = 134.18$, 119.90, 96.12, 82.21, 72.45, 72.13 ppm.

*5,6-Dideoxy-L-arabino-hex-5-enofuranose* (**15**: $C_6H_{10}O_4$)

Colorless syrup; $R_f = 0.18$ ($CHCl_3$:MeOH = 9:1); 1:1 mixture of $\alpha$:$\beta$ anomers; $^1$H NMR ($D_2O$, 500 MHz, both anomers): $\delta = 5.91$–$5.80$ (m, 2H), 5.38–5.23 (m, 5H), 5.20 (d, $J = 3.0$ Hz, 1 H) 4.38–4.35 (m, 1 H), 4.07–3.91 (m, 4H), 3.84–3.82 (m, 1 H) ppm; $^{13}$C NMR ($D_2O$, 125 MHz, both anomers): $\delta = 136.92$, 135.49, 120.18, 119.63, 101.44, 95.45, 84.23, 82.57, 82.18, 80.03, 78.20, 76.38 ppm.

## Acknowledgments

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