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Efficient alternative for the reduction of *N*-trichloroacetyl groups in synthetic chondroitin oligosaccharide intermediates

Aude Vibert, Chrystel Lopin-Bon, Jean-Claude Jacquinet *

Institut de Chimie Organique et Analytique, UMR 6005 Université d'Orléans et CNRS, UFR Sciences, Université d'Orléans, BP 6759, 45067 Orléans Cedex 2, France

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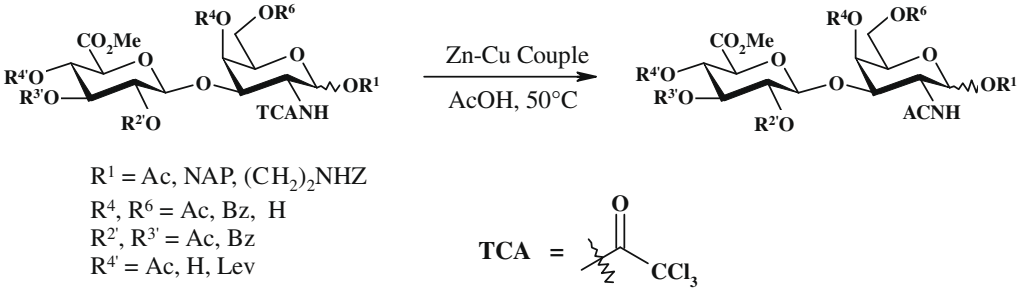
ABSTRACT

An efficient alternative for the reduction of *N*-trichloroacetyl groups in chondroitin oligosaccharides is reported. It involves the use of Zn–Cu couple in acetic acid, and was successfully applied to a large panel of synthetic intermediates useful for the preparation of chondroitin oligomers, a class of natural products with numerous relevant biological functions.

Chondroitin sulfate (CS) belongs to the family of proteoglycans, an important class of biomolecules involved in numerous relevant biological processes.[1] They are heterogenous linear polysaccharides constituted of a disaccharide-repeating unit composed of D-glucuronic acid (D-GlcA) and 2-acetamido-2-deoxy-D-galactose (D-GalNAc) arranged in the sequence [→4)-β-D-Glc*p*A-(1→3)-β-D-Gal*p*NAc-(1→]$_n$, and contain, on average, one sulfate group per disaccharide unit. Up to date, two main strategies have been reported for the preparation of the D-GalNAc residue in such molecules. The first one was based on the azidonitration of D-galactal[2] which provided a 2-azido-2-deoxy group that was further reduced and transformed in the last steps of the synthesis into a 2-acetamido-2-deoxy group.[3a–d] The second strategy involved the use of a 2-deoxy-2-trichloroacetamido group, which acted as a powerful stereocontrolling auxiliary in the synthesis of 1,2-*trans*-2-amino-2-deoxy sugars.[4a–e] This later was reduced into its *N*-acetyl congener under radical conditions using toxic tributylstannane.[5] However, in some cases, the radical reduction did not go to completion and mono- or dichloroacetamide intermediates were isolated.[6] In addition, the yields are sometimes not reproducible and difficulties in eliminating tin species are often encountered.[4e] Since classical basic conditions such as the use of $NaBH_4$/EtOH[7] or KOH/EtOH[8] which removed the trichloroacetyl group and generated the free amine cannot be employed when ester groups were used in the synthetic plan, we turn out our attention toward a mild and less toxic method using Zn–Cu couple in acetic acid, a technique still reported for trichloroacetyl dehalogenation on sugar structures,[9] but that, to the best of our knowledge, was never



Scheme 1. Reduction of the *N*-trichloroacetyl group in various chondroitin derivatives.

* Corresponding author. Tel.: +33 238 417072; fax: +33 238 417281.
E-mail address: Jean-Claude.Jacquinet@univ-orleans.fr (J.-C. Jacquinet).

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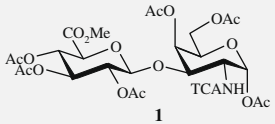
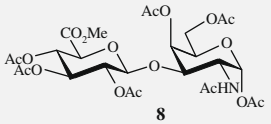
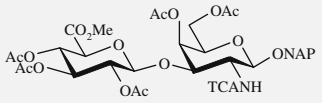
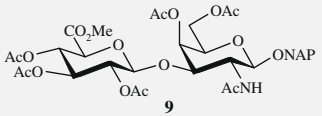
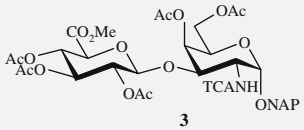
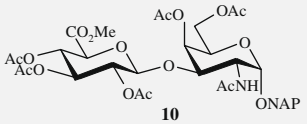
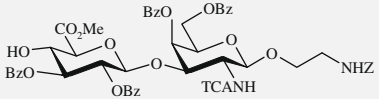
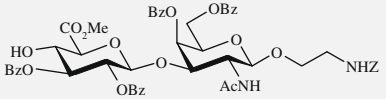
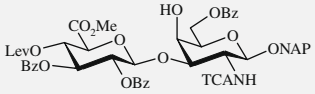
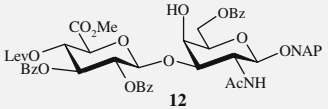
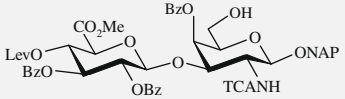
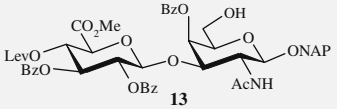
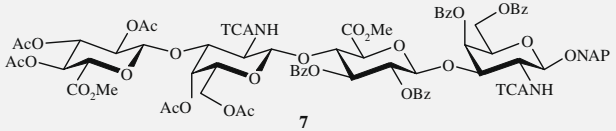
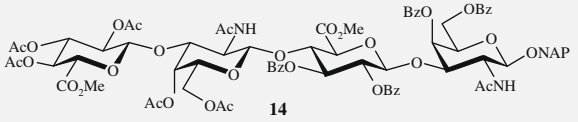
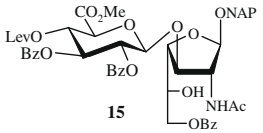
Table 1
N-Acetylated chondroitin derivatives produced via Scheme 1

Entry	Starting material	Product	Conditions	Yield (%)
1	 **1**	 **8**	24 h at 50 °C	95
2	 **2**	 **9**	24 h at 50 °C	77
3	 **3**	 **10**	24 h at 50 °C	92
4	 **4**	 **11**	24 h at 50 °C	98
5	 **5**	 **12**	24 h at 50 °C 5 h at 50 °C	48[a] 71
6	 **6**	 **13**	7 h 30 min at 50 °C	85
7	 **7**	 **14**	24 h at 50 °C	93

[a] Mixture of products with 22% yield of furanoside **15** side-product.


15

applied to complex molecules such as CS oligomers. Classical reduction conditions[10] were tested on several chondroitin oligosaccharides which have been used as key intermediates during CS oligomer syntheses.[4a–c,11] These molecules are equipped with different protective groups at the anomeric center, and bear diverse ester (acetate, benzoate, and levulinate) or hydroxy groups on the other positions (Scheme 1).

The results of these studies are reported in Table 1. The reduction reaction was first attempted on peracetylated disaccharide derivative **1** (entry 1). The reaction proceeded smoothly and was complete within 24 h at 50 °C giving the acetamide **8** in 95% yield. Next were tested glycosides **2** and **3** (entries 2 and 3), which differ only by the chirality at the anomeric center with a bulky 2-naphthylmethyl group in the vicinity of the trichloroacetyl group. Both reductions proceeded well and the acetamides **9** and **10**, respectively, were isolated in good yields. More interesting is the reduction of **4** (entry 4) which possesses a benzyl carbamate and a free hydroxy group. In that case, neither cleavage of the carbamate nor acetylation of the hydroxyl was observed. When these conditions were applied to disaccharide derivative **5** (entry 5) having a free hydroxyl group at C-4 of the D-galactosamine unit, a mixture of products was obtained in which the desired acetamide **12** could be isolated in only 48% yield. A major side-product was formed and unambiguously identified through ^{1}H and ^{13}C NMR as the furanoside **15**.[12] Such a modification of structure resulting from ring contraction at the D-galactosamine unit was already observed on the parent molecules under acidic conditions.[4d] We assumed that the zinc salts slowly released during the reaction acted as a Lewis acid which led to transient open-chain oxonium ion which reacted further with the free 4-OH group to provide the furanoside **15**. However, shortening the reaction time to 5 h allowed the isolation of acetamide **12** in an improved 71% yield. Starting from disaccharide **6** having a free hydroxy group at C-6 and a benzoate ester at C-4, no side-product was formed, and acetamide **13** was isolated in 85% yield. Both compounds **12** and **13** were now ready for subsequent O-sulfonation. More relevant is the reduction of tetrasaccharide **7** (entry 7) bearing two trichloroacetyl groups, which gave diacetamide **14** in 93% yield, whereas the radical-mediated reductive dehalogenation allowed the isolation of **14** in only 62% yield. As a general rule, the yields of the reactions are 20–30% superior to those obtained by the tin procedure.

In conclusion, these mild conditions using an operationally simple procedure worked well on a large panel of chondroitin derivatives with one or more trichloroacetyl group(s) and compared well with those previously reported,[5] and could be applied to other synthetic intermediates bearing a 2-deoxy-2-trichloroacetamido group in the synthesis of other members of the biologically relevant GAG's family such as hyaluronic acid and dermatan sulfate.

Acknowledgments

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Supplementary data

Supplementary data (Protocols for each reaction and ^{1}H and ^{13}C NMR data for reduced products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.005.

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10. *General procedure for the reduction reaction*: Zn–Cu couple (Acros Organics, 100 mg, 1.5 mmol) was added portionwise to a solution of the starting material (0.1 mmol) in pure acetic acid (1.5 mL) at 50 °C under Ar, and the mixture was stirred for the allotted time (see Table 1), cooled, filtered through a pad of Celite®, and concentrated. The resulting residues were directly purified by flash-silica chromatography.
11. Vibert, A. PhD Thesis, University of Orléans (France), November 2009.
12. See Supplementary data.