Tetrahedron 67 (2011) 8825–8850

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Tetrahedron report number 953

Modern methods for shortening and extending the carbon chain in carbohydrates at the anomeric center

Rune Nygaard Monrad[a], Robert Madsen[b,*]

[a] *Novozymes A/S, Krogshøjvej 36, 2880 Bagsværd, Denmark*
[b] *Technical University of Denmark, Department of Chemistry, 2800 Kgs. Lyngby, Denmark*

ARTICLE INFO

Article history:
Received 7 August 2011
Available online 24 August 2011

Keywords:
Aldol condensations
Anomeric center
Carbohydrates
C–C bond formation
Organometallic reactions
Radical reactions

Contents

---

* Corresponding author. Tel.: +45 4525 2151; fax: +45 4593 3968; e-mail address: rm@kemi.dtu.dk (R. Madsen).

0040-4020/$ – see front matter
doi:10.1016/j.tet.2011.08.047

---

1. Introduction

Carbohydrates are the most abundant of the biomolecules in nature, and responsible for two-thirds of the carbon found in the biosphere.[1] In living organisms carbohydrates play important roles in a vast array of biological processes. All cells are coated with a layer of complex carbohydrates, which take part in cell adhesion, cell growth, and intercellular communication.[2] About half of all human proteins are glycosylated and the carbohydrate moieties ensure correct folding, increased stability, and provide epitopes for recognition.[3,4] The carbohydrate-processing enzymes glycosidases and glycosyl transferases control the hydrolysis and the formation of the glycosidic linkage in naturally occurring oligosaccharides. The glycosidases have been the target for several carbohydrate-derived drugs that act as enzyme inhibitors.[5] Contrary to inhibiting biological processes, carbohydrate-based vaccines act in the opposite manner since oligosaccharides conjugated to proteins are able to induce an immune response leading to production of specific antibodies.[6]

The importance of carbohydrates in biological processes as well as the fact that carbohydrates are cheap and easy available have stimulated much interest in synthetic carbohydrate chemistry. The complex structure of carbohydrates makes their synthetic chemistry more diverse than the chemistry of the other two major biomolecules, the amino acids, and the nucleotides. Carbohydrate synthesis mainly involves protecting-group transformations, glycosylation reactions, oxidations/reductions and C—N/C—C bond formation.[7] In the latter category, methods for adjusting the length of the carbon chain in monosaccharides are very useful in order to broaden the synthetic scope of carbohydrates. Smaller carbohydrates are valuable chiral building blocks in the synthetic laboratory while a number of chain-elongated carbohydrates, so-called higher-carbon sugars, are naturally occurring compounds with important biological functions.[8–10] Developing methods for shortening and extending the carbon chain in carbohydrates has been a subject in carbohydrate chemistry for more than a century, and the literature up to 1997 is covered in the book ‘Monosaccharide Sugars: Chemical Synthesis by Chain Elongation, Degradation, and Epimerization’ (Academic Press, 1998).[11] The purpose of the present review is to provide an overview of the synthetic methods for shortening and extending the carbon chain in carbohydrates, which have been presented since 1997.[12] The focus will be on reactions that take place at the anomeric center of aldoses and ketoses.

2. Methods for shortening the carbon chain in carbohydrates

2.1. Chain shortening by radical methods

2.1.1. Ruff degradation. The available methods for shortening the chain in unprotected monosaccharides are sparse. The Ruff degradation, which has been known since 1898,[13] converts salts of aldonic acids into aldoses with loss of one carbon atom. The reaction is performed with hydrogen peroxide in alkaline solution in the presence of Fe(III) or Cu(II) salts, where the latter are the most efficient.[14] Due to its importance in the preparation of pentoses, the Ruff degradation continues to receive considerable attention.

The reaction generally occurs in a moderate yield[11] and, since one of the major disadvantages in the Ruff degradation is the separation of the product from large quantities of metal salts, work has been done to cleave carbon dioxide from the aldonate electrochemically or by the use of catalytic amounts of the metal. Jiricny and Stanek utilized a fluidized-bed electrode cell for the production of D-arabinose in approximately 70% yield from sodium D-gluconate without adding any chemical oxidants.[15] The production of D-arabinose from calcium D-gluconate has been achieved in 63% yield by Germain and co-workers using hydrogen peroxide and catalytic amounts of Cu(II)-exchanged zeolites.[16] During the reaction, copper was found to leach from the zeolite and, once the aldonic acid was consumed, copper precipitated on the zeolite again. The catalyst could be recycled twice thereby achieving the advantages of heterogeneous catalysis, although copper was in solution during the reaction.[16]

Several different mechanisms for the Ruff degradation have been proposed over the years, and these have recently been critically reviewed by Stapley and BeMiller.[14] Based on the experimental observations under a variety of conditions they favor a reaction mechanism with two successive one-electron oxidations (Scheme 1). The aldonate **1** is oxidized to an acyloxy radical **2**, which upon loss of carbon dioxide and subsequent oxidation produces a carbocation **3**, that is, captured by the solvent. This mechanism is believed to be valid both in the electrochemical Ruff degradation and in the classical versions, where the anode is