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Reductive Deamination by Benzyne for Deoxy Sugar Synthesis Through a Domino Reaction

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Benzyne was developed as a reducing agent in the key step of converting amino sugars and ketoses into deoxy sugars, which occur widely in natural products. Many deoxy sugars exhibit antibiotic and anticancer activities, and furthermore, they play essential biological roles. By treatment with CS_2 and then Ac_2O, amino sugars and ketoses were converted into the corresponding 1,3-thiazolidine-2-thiones. In the key step, these intermediates were treated with 2-trimethylsilylphenyl triflate (2.0 equiv.) and CsF (3.0 equiv.) in MeCN at 25 °C to produce acyclic enol acetates in 60–63% yields. Saponification of the enol acetates with NaOMe/MeOH followed by intramolecular cyclization afforded the target 2-deoxy sugars. The key step of the reductive deamination involved a domino 1,2-elimination/[3+2]-cycloaddition/retro [3+2]-ring-opening sequence. The generality of this new method was proven by the use of various substrates, including pentoses, hexoses, monosaccharides, disaccharides, aldoses, and ketoses.

Deamination, the removal of an amine group from a molecule, plays an important role in chemical transformations and biological systems.[1] Chemical reagents developed for this purpose[2] include copper(II) halides along with alkyl nitrites;[3] HCO_2H/acetic anhydride (Ac_2O) followed by $POCl_3$/Et_3N and then tributyltin hydride;[4] hydrogen peroxide along with tetrabutylammonium iodide as the catalyst;[5] isopropyl *N*,*N*-difluorocarbamate;[6] nitrosyl acetate;[7] nitrosyl tetrafluoroborate;[8,9] *p*-nitrophenyl formate, Ac_2O, $POCl_3$/Et_3N, and tributyltin hydride in sequence;[10] samarium iodide;[11] sodium borohydride along with 2,3,5,6-tetraphenylpyrylium tetrafluoroborate;[12] sodium nitrite;[13] and zinc dichromate trihydrate.[14] Deamination of amino acids and proteins can proceed through an oxidative process[2] by using molecular oxygen in the presence of a D-amino acid oxidase, lysine cyclodeaminase, L-lysine oxidase, pyridoxal phosphate cofactor,[15] and so forth. Deamination of DNA bases by nitrous anhydride (N_2O_3)[16] can occur spontaneously to generate uracil, hypoxanthine, and xanthine.

It was our plan to apply a domino sequence for the deamination of compounds in the synthesis of deoxy sugars under mild and neutral conditions. Deoxy sugars constitute an important class of carbohydrates that occur widely in natural products. Prominent examples include 2-deoxy-D-*erythro*-pentoses in DNA and deoxyhexoses in antibiotics and anticancer agents such as anthracyclines, angucyclines, aureolic acid, cardiac glycosides, macrolides, and pluramycins.[17] Moreover, the deoxy sugar components in different drugs are essential for their pharmacology and biological activities.[18] As found in lipopolysaccharides, glycoproteins, and glycolipids, a wide variety of deoxy sugars therein play versatile biological roles. Furthermore, some 2,6-dideoxy sugars have been found in antibiotics isolated from *Streptomyces spp.* and in cardiac glycosides isolated from plant sources.[18] Other prominent examples include chromomycin A3 (**1**; Figure 1),[19] which is an antitumor drug produced by *Streptomyces griseus* subsp. *griseus*. Landomycin A (**2**; Figure 1),[20] isolated from a culture broth of *Streptomyces cyanogenus*, is an antibiotic. Both representative examples con-

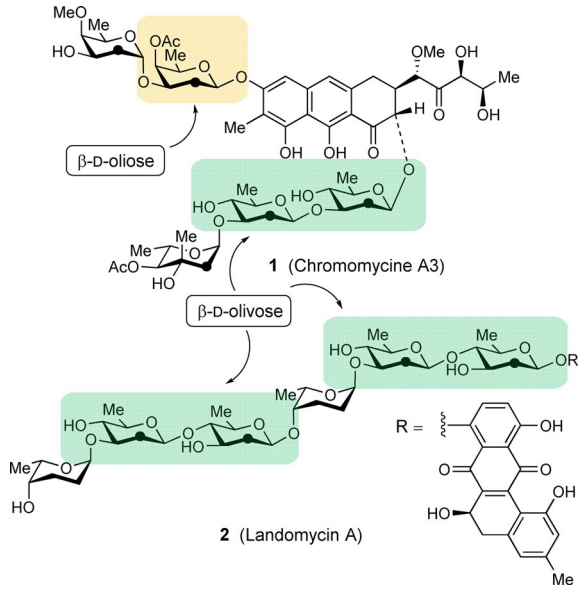

Figure 1. Structures of compounds **1** and **2**.

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tain a β-D-olivose unit. Chromomycin A3 (**1**) also contains a β-D-oliose unit.

Some reagents are used to perform "oxidative deamination" for the conversion of an amino group into a carbonyl group. Representative examples include hydrogen peroxide, molecular oxygen, nitrous anhydride, nitrosyl tetrafluoroborate, pyridoxal phosphate, and zinc dichromate trihydrate.[2] Close scrutiny of the literature reveals that only a limited number of reagents are used to accomplish "reductive deamination." Reagents for this type of reaction include isopropyl *N*,*N*-difluorocarbamate,[6] samarium iodide,[11] and sodium borohydride.[12]

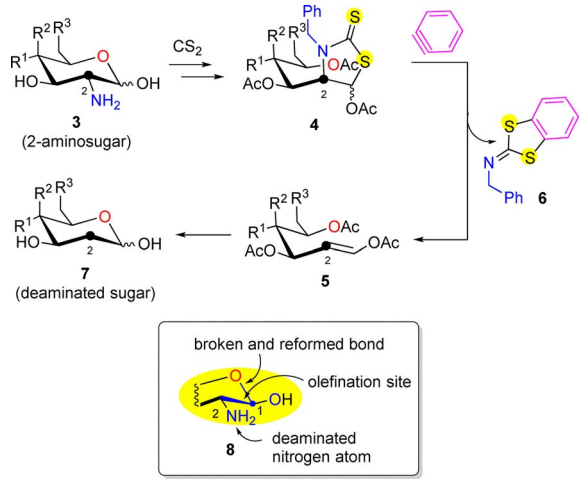
The reactive benzyne species[21] is considered by us as an ideal candidate for reductive deamination for two reasons. First, it can be generated through fluoride displacement in 2-silylphenyl triflate under mild conditions.[22] Second, it was previously successfully applied in the reductive deoxygenation of carbohydrates[23] and in reductive insertion into the S=O bond of DMSO, as reported by Chen et al.[24] As an oxidized form of benzene, benzyne was postulated to be able to act further as a "reducing agent" to remove a nitrogen atom from organic substrates.

Herein, we report our findings on the feasibility and generality of using benzyne in the reductive deamination reaction. This domino reaction was successfully applied in the synthesis of deoxy sugars from amino sugars and ketoses.

The synthetic methods used for the conversion of sugars into deoxy sugars often involve reductive removal of the oxygen atom of the hydroxy group by substitution of the corresponding sulfonates with a hydride[25] or an alkyl group.[26] The Barton method involving the use of *S*-methyl dithiocarbonates with tributyltin hydride offers an alternative and efficient route.[27,28] Moreover, the Fischer–Zach reaction allows the conversion of glycosyl halides into glycals with zinc dust in acetic acid. These unsaturated sugars may undergo electrophilic addition at the C2 position to give 2-deoxy sugars.[29,30] Alternatively, biosynthetic transformations with the aid of enzymes can also deoxygenate sugars.[31] Serving as the starting materials in this newly developed transformation, amino sugars are popular compounds. They occur widely in nature and are found in a great variety of polysaccharides, glycolipids, mucoproteins, nucleotides, teichoic acids, and antibiotics.[32] Moreover, many amino sugars are commercially available.

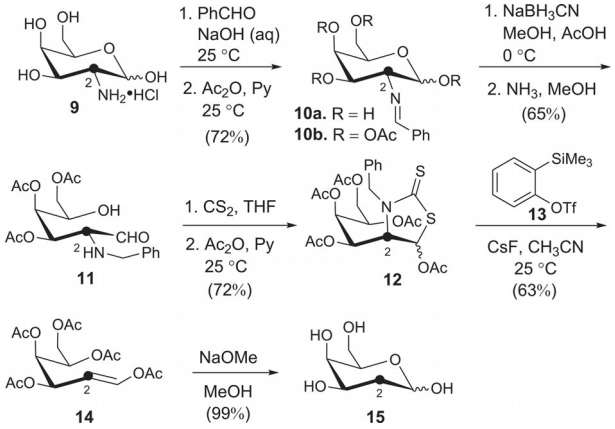
The strategy shown in Scheme 1 accounts for our design of a new "reductive deamination" reaction that can be applied to the synthesis of deoxy sugars from amino sugars. It involves the conversion of amino sugars **3** into thiazolidine-2-thiones **4** with carbon disulfide. Then, benzyne is used to "extract" the –N(C=S)S– moiety in **4** to give enol acetates **5** and 2-imino-l,3-benzodithiole **6** as a byproduct. Finally, removal of the acetyl groups followed by cyclization provides desired deoxyaldoses **7**. Overall, the nitrogen atom attached to the C2 atom of **8** is expelled, a double bond is formed between C1 and C2, and the endocyclic O–C bond is cleaved and then regenerated.

As proof for the feasibility of the new reductive deamination strategy, an example was put into practice. Conversion of commercially available (+)-D-galactosamine hydrochloride (**9**) into benzylamine aldose **11** via intermediates **10a** and **10b** in-



Scheme 1. Strategy for the deamination of amino sugars by benzyne.

volved formation of a Schiff base with benzaldehyde, protection of the hydroxy groups with Ac_2O, reduction of the Schiff base with $NaBH_3CN$, and selective deprotection of the anomeric acetate with NH_3 (see Scheme 2). Then, aminoaldose **11** was

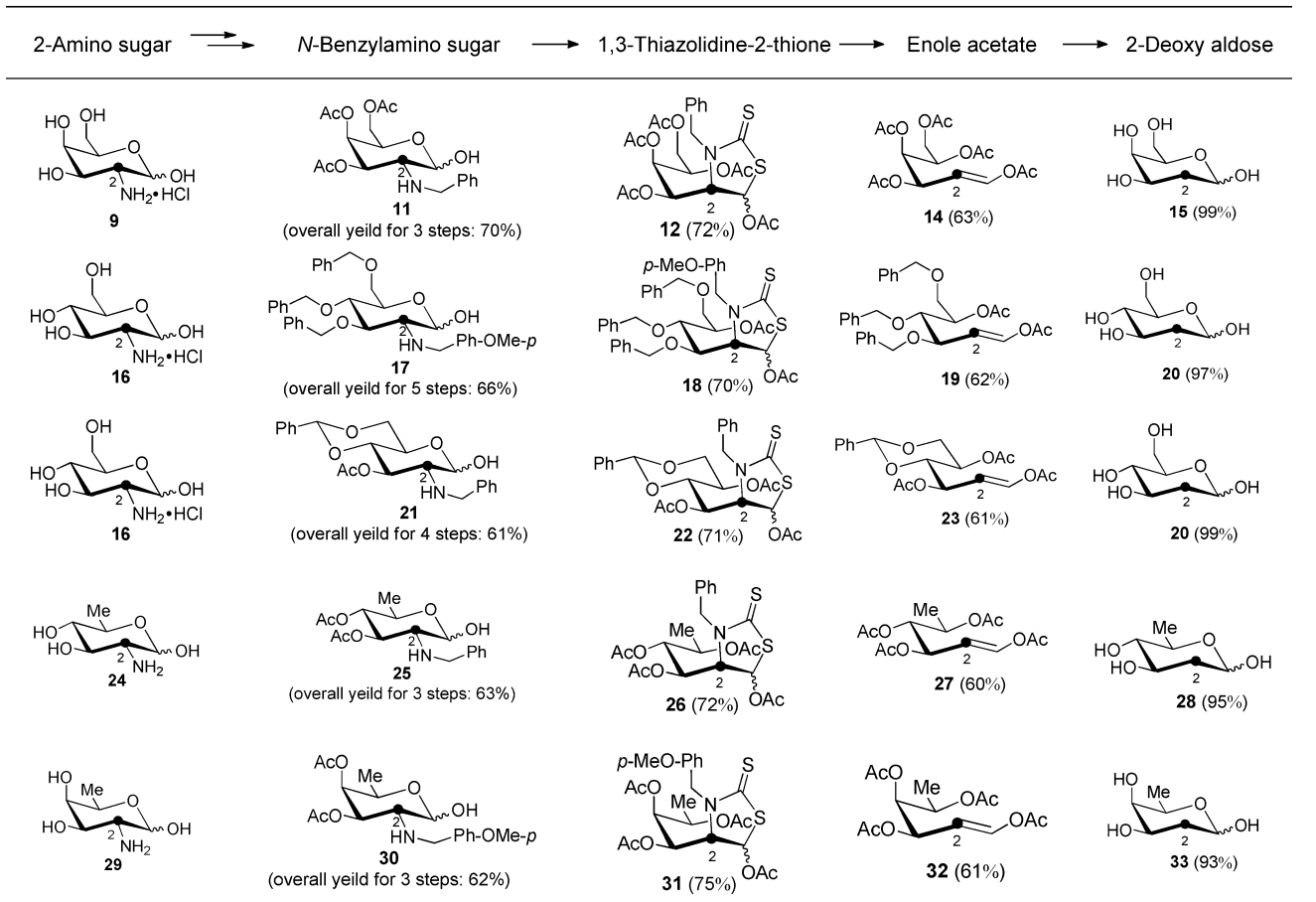


Scheme 2. Detailed procedure for the reductive deamination of galactosamine hydrochloride (**9**).

treated with CS_2 in THF for 12 h and then with Ac_2O in pyridine (Py) to produce 1,3-thiazolidine-2-thione **12** in 72% yield. Isolated thione **12** was then mixed with 2-silylphenyl triflate (**13**, 2.0 equiv.) and CsF (3.0 equiv.) in MeCN at 25 °C for 60 min. Acyclic enol acetate **14** was isolated in 63% yield, and it was treated with NaOMe in MeOH. Accordingly, desired (+)-D-2-deoxygalactose (**15**) was generated in almost quantitative yield. In the entire transformation of **9** → **15**, the nitrogen atom attached to the C2 carbon of galactosamine (**9**) was expelled.

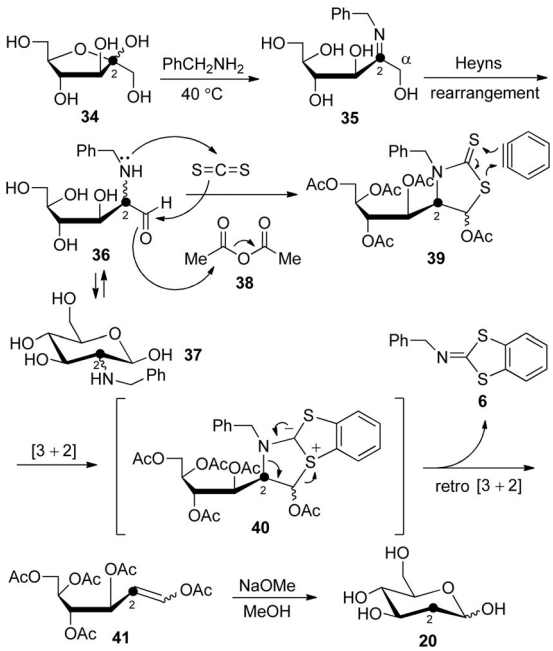
Many conditions were examined to optimize the yield of the benzyne-induced deamination reaction for the conversion of 2-thione **12** into enol acetate **14**. Different kinds of fluoride sources (Bu_4NF, KF, and CsF) with various equivalents (2.0–3.0), solvents (MeCN, Et_2O, and THF), temperatures (0–80 °C), and reaction times (0.50–8.0 h) were tested. The best combination involved the use of CsF (3.0 equiv.) with triflate **13** (2.0 equiv.) in

Table 1. Intermediates and yields for the conversion of 2-amino sugars into 2-deoxyaldoses.



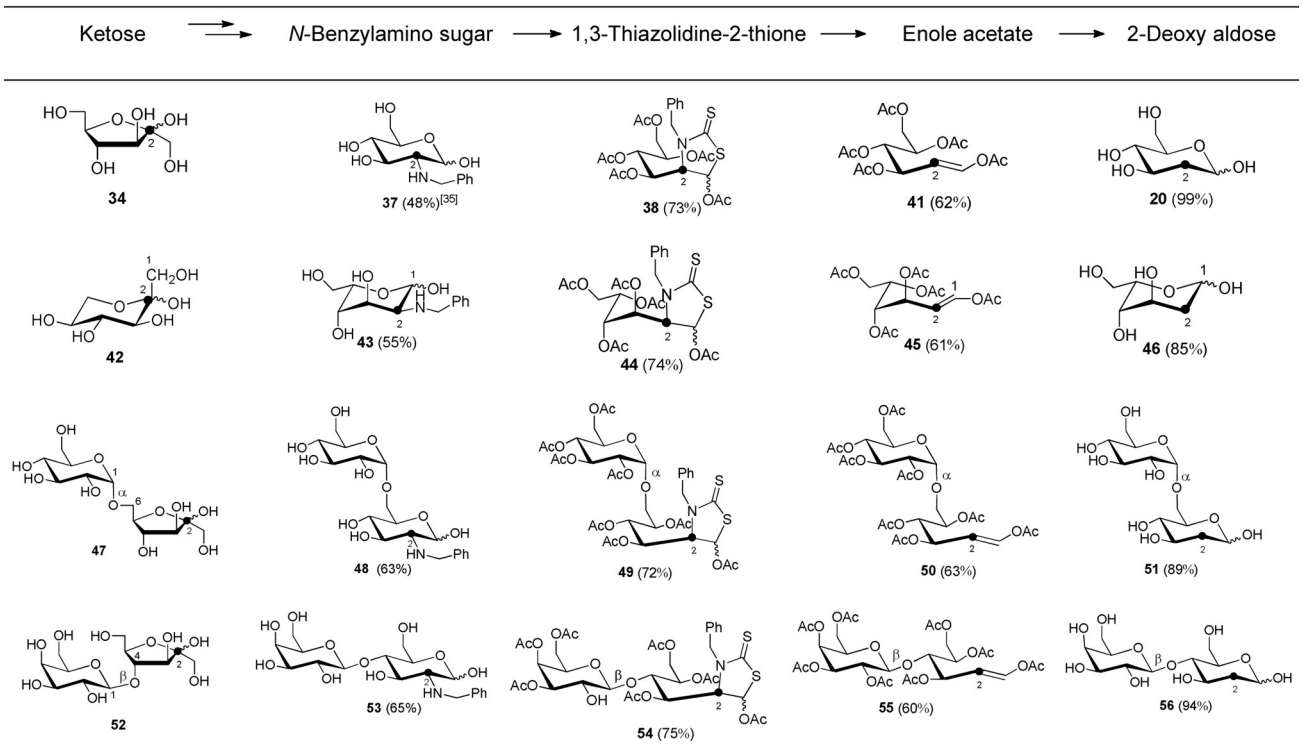
MeCN at 25 °C for 1.0 h. In Table 1, five examples of the same transformation as that displayed in Scheme 1 are listed. Their key steps are the benzyne-induced deaminative olefination, including the conversions of **12**→**14**, **18**→**19**, **22**→**23**, **26**→**27**, and **31**→**32**. Protection of the OH groups in the form of an acetal (e.g. **22**), acetate (e.g. **12** and **26**), benzyl (Bn) ether (e.g. **18**), and *p*-methoxybenzyl ether (e.g. **18**) allowed formation of the deaminated products in good yields.[33] In the entire transformations, the reaction conditions were mild enough to prevent undesired isomerization from occurring at carbon centers of the sugars.

α-Hydroxy imines (e.g. **35**), prepared from 2-ketoses (e.g. **34**) and primary amines, can undergo the Heyns rearrangement[34] to produce stable α-amino aldehydes (e.g. **36**). Their cyclic hexopyranose forms (e.g. **37**) belong to the class of 2-amino sugars, which were applied successfully as starting materials in the synthesis of a 2-deoxy sugars. A representative example is shown in Scheme 3; the key intermediates, products, and yields of more examples are listed in Table 2. These results indicate that the reductive deamination reaction could be successfully extended to the conversion of 2-ketoses into 2-deoxy sugars with a complex disaccharide structure, such as isomaltulose (**47**) and lactulose (**52**).



Scheme 3. Conversion of ketose **34** into deoxyglucose **20** via 2-aminoaldose **36**, and the mechanism for the deamination key step.

Table 2. Intermediates and yields in the conversion of 2-ketoses into 2-deoxyaldoses via 2-amino sugars.



A cogent mechanism for the newly developed reductive deamination by use of benzyne is depicted in Scheme 3. The addition of amino aldehyde **36** to carbon disulfide followed by Ac_2O (**38**) gives 1,3-thiazolidine-2-thione **39**. Then, its –C(=S)S– moiety adds onto benzyne, generated in situ by 1,2-elimination of 2-silylphenyl triflate (**13**) with CsF, through a [3+2]-cycloaddition mode to give cyclic ylide **40**. Subsequently, a retro [3+2] reaction takes place to afford ring-opened enol acetate **41** as the desired product and 2-imino-l,3-benzodithiole (**6**) as a byproduct.

After the conversion of 2-thione **39** into enol acetate **41**, the oxidation state of the C2-NBn carbon atom of **39** decreases and that of the *sp* carbon atoms of benzyne increases. Thus, benzyne is oxidized and acts as a reducing agent; moreover, thione **39** loses an amino group. Therefore, the benzyne species functions as a reductive deamination agent.

In addition to the –C(=S)S– moiety, the possibility exists for the –C(=S)N– moiety in 2-thione **39** to react with benzyne. Nevertheless, both pathways would lead to the same enol acetate, **41**, as the desired product.

Saponification of the enol acetates listed in Tables 1 and 2 with sodium methoxide in methanol gave the corresponding 2-dexoy aldoses in excellent yields. Taking all of the steps into account, both 2-amino sugars and 2-ketoses underwent domino deamination as the key step to give deoxy aldoses as the final products.

In conclusion, active benzyne generated in situ was developed as a reducing reagent for deamination. This method was applied successfully as the key step in the synthesis of deoxy sugars in an optically active form from 2-amino sugars and 2-ketoses. The reaction conditions were compatible with *O*-glycosides, acetals, the acetyl group, the enol acetate functionality, and the benzyl group. Except for the C1 and C2 atoms, all of the remaining stereogenic centers in the carbohydrate starting materials retained their original configurations.

This new reductive deamination method proceeds through a domino reaction involving 1,2-elimination to form benzyne, a [3+2]-cycloaddition reaction between benzyne and a 1,3-thiazolidine-2-thione, and a retro [3+2]-ring-opening reaction of an ylide to afford an enol acetate. This protocol provides two new avenues to optically active deoxy sugars under mild conditions. In the near future, more benzyne-induced reactions proceeding in a domino fashion will be developed for the efficient synthesis of various types of functional compounds.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: benzyne · deamination · deoxy sugars · domino reactions · reduction

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