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Catalytic conversions of diazosugars

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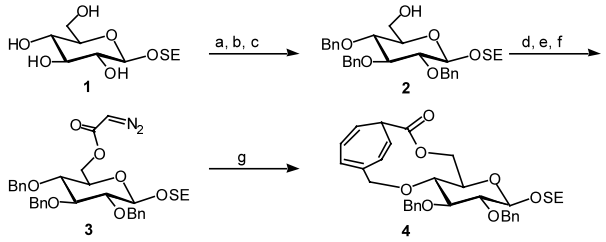
Abstract—Catalytic diazo decomposition chemistry was explored with novel diazoacetate functionalized carbohydrates. In both glucose and galactose derivatives, aromatic cycloadditions with the benzyl protecting groups proved to be most favorable reactions. Replacing the benzyl groups by methoxy groups in the glucose system led to formation of 'carbene dimers'. © 2002 Elsevier Science Ltd. All rights reserved.

Chemistry involving catalytic metal carbene transformations has proven to be a powerful and versatile area.[1] Many highly selective reactions, using diazocompounds as starting materials and preferentially dirhodium complexes as catalysts, have been developed. These include cyclopropanations, ylide generation and their following reactions and insertion reactions. Despite the rich toolbox that has been generated very few applications of this chemistry have been directed towards carbohydrates.[2] Considering that metal carbene intermediates can add to or insert into various bonds present in carbohydrate derivatives, the application of carbenoid chemistry may give rise to novel compounds, not accessible via alternative methods. The synthesis of novel carbohydrate derivatives is an important goal. Due to the expanding knowledge of the roles that carbohydrates play in important biological processes, unnatural carbohydrate derivatives may have potential biomedical applications due to interference with these processes.[3]

In order to explore some of the issues mentioned above we decided to incorporate a diazoacetate moiety into a carbohydrate. We chose glucose as the carbohydrate and the C(6) oxygen for attachment of the diazoacetate group. Glucose derivative **1**, containing the 2-(trimethylsilyl)ethyl (OSE) group at the anomeric oxygen,[4] was the starting material and was treated with trityl chloride in order to protect selectively the C(6) hydroxyl group (Scheme 1). Following this, the remaining free hydroxyls were benzyl protected and the C(6) hydroxyl group was liberated by treatment with acid to yield **2**. Reaction of **2** with diketene resulted in the corresponding acetoacetate, required for the subsequent diazo transfer with MsN_3. Deacylation by LiOH led to the desired diazo compound **3**.[5]

In order to explore its catalytic decomposition chemistry, diazo compound **3** was dissolved in CH_2Cl_2 and added slowly to a solution containing a catalytic amount of $Rh_2(OAc)_4$. Three new products were formed, all with the same molecular weight corresponding to the molecular weight of **3** minus dinitrogen (m/z 613 $M+Na^+$) according to the electrospray mass spectra. The major product was identified as cycloheptatriene **4** and could be isolated in 45% yield. A detailed analysis of its COSY spectra confirmed the 1,4 substitution pattern of the cycloheptatriene ring versus the alternative 1,2 and 1,3 patterns.[6] The ^1H NMR spectrum suggested that the reaction had taken place with the C(4) benzyloxy group since for **4** the chemical shifts



Scheme 1. *Reagents and conditions*: (a) Ph_3CCl, DMAP, pyr, 80°C, 3 h; (b) BnBr, NaH, DMF, 14 h; (c) AcOH/EtOH 1:1, 80°C, 12 h, 47% (3 steps); (d) diketene, NEt_3, THF, 6 h; (e) MsN_3, NEt_3, THF, 20 h; (f) LiOH, THF/H_2O, 14 h, 43% (3 steps); (g) $Rh_2(OAc)_4$, CH_2Cl_2, 22 h, 45%.

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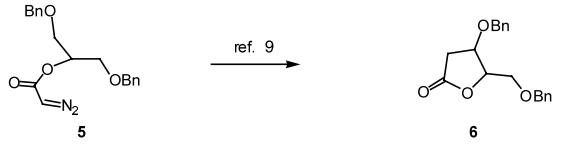
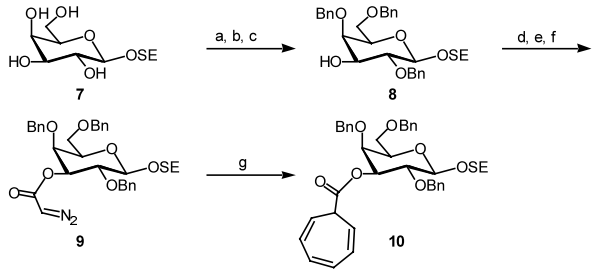
of H–C(2) and H–C(3) were close to the same value (within 0.1 ppm) as in **3**, however the H–C(4) signal had moved from 3.52 to 3.80 ppm. A NOESY spectrum confirmed this since the observed NOEs clearly allowed assignment of the benzyloxy groups at C(2) and C(3), and also showed signals between the cycloheptatriene ring and the C(4)-linked OCH_2 moiety. The reaction leading to product **4**, was an intramolecular aromatic cycloaddition that proved to be more favorable than a C–H insertion reaction into one of the available C–H bonds of the pyranose ring. For the aromatic cycloaddition alternative addition products involving the other benzyloxy groups, or other positions on the C(4) benzyloxy group seemed conceivable as well. Indeed ^{1}H NMR spectra of the two minor products both showed the characteristic signals of the cycloheptatriene unit. In order to attempt to influence the reaction outcome, reactions were also run in the presence of dirhodium(II) perfluorobutyrate ($Rh_2(pfb)_4$) and dirhodium(II) caprolactamate ($Rh_2(cap)_4$), which should lead to more and less reactive intermediate metal carbenes, respectively, in comparison to $Rh_2(OAc)_4$. Use of these alternative catalysts has been shown in several cases to give rise to vastly different selectivities.[1] In the reaction with **3**, however, all three catalysts gave the same products in close to the same ratios.

Although the aromatic cycloaddition is known to be a good reaction, especially with $Rh_2(pfb)_4$ as a catalyst,[7] C–H insertion reactions into H–C(4), H–C(5) or H–C(6) of **3** and also the Stevens Rearrangement[8] seemed possible as well. In an attempt to create a geometry as favorable as possible for a C–H insertion reaction, a reported successful C–H insertion reaction was used in the design of the next diazosugar. The reaction involved was the high yield cyclization of **5**, a diazocompound based on glycerol. The cyclization of this compound gave in good yield the 5-membered lactone **6** with catalysis by dirhodium(II) carboxamide catalysts (Scheme 2).[9]

In order to keep important aspects such as the expected ring size and electronic activation (by donating substituents such as OBn) the same, galactose derivative **9** with its diazoacetate moiety linked to the C(3) oxygen was selected for synthesis (Scheme 3). Despite the similarities between **5** and **9** obvious differences are the conformational restrictions in **9** and the fact that the targeted insertion sites have a higher degree of alkyl substitution. The latter aspect actually makes the sites more reactive for insertion.[1] In the synthesis of **9**, galactose **7**[4] was regioselectively protected with a *p*-methoxybenzyl group at the C(3) oxygen via a dibutylstannylene acetal,[10] protection of the other hydroxyls with benzyl groups was followed by selective cleavage of the *p*-methoxybenzyl group using cerium(IV) ammonium nitrate[10] to yield **8**. As before, the liberated hydroxyl was elaborated into the diazoacetate unit of **9** using the three-step protocol with diketene, MsN_3 and LiOH, respectively. Catalytic diazo decomposition of **9** in the presence of $Rh_2(OAc)_4$ in CH_2Cl_2 resulted in the



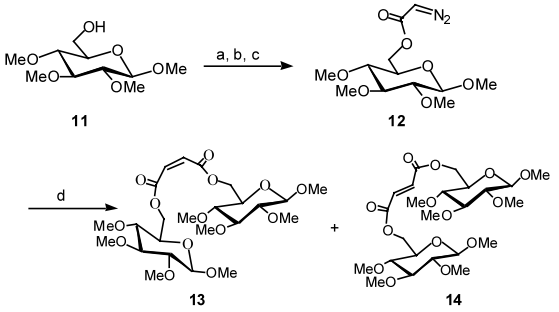
Scheme 2. Reported favorable C–H insertion reaction.



Scheme 3. *Reagents and conditions*: (a) *n*-Bu_2SnO, *p*-OMeBnCl, PhH, 80°C, 2 h, (76%); (b) BnCl, NaH, DMF, 14 h, (67%); (c) CAN, CH_3CN/H_2O, 4.5 h, (82%); (d) diketene, NEt_3, THF, 14 h; (e) MsN_3, NEt_3, THF, 14 h; (f) LiOH, THF/H_2O, 5 h, 72% (3 steps); (g) Rh_2OAc_4, PhH, 16 h.

disappearance of the starting material and the appearance of three compounds. No true major product was observed. The mixture was (partially) purified by column chromatography and the resulting fractions were analyzed by electrospray mass spectrometry and NMR. All samples showed only a single MS signal at m/z 613 ($M+Na^+$), as was expected for all insertion or addition products. ^{1}H NMR spectra of the samples showed the characteristic cycloheptatriene signals between 5.7 and 6.8 ppm, but the specific substitution pattern could not be identified. This shows that again the aromatic cycloaddition to the benzyl protecting groups was the most favorable reaction and no significant amounts of products derived from C–H insertion could be detected. Reactions with the alternative catalysts $Rh_2(pfb)_4$, and $Rh_2(cap)_4$ gave similar reaction profiles. The ease of cycloheptatriene formation could also be illustrated by running the $Rh_2(OAc)_4$ catalyzed reaction in benzene, which gave cycloheptatriene **10** as the only product.

The previous results showed that C–H insertion into the pyranose C–H bonds was not a favorable reaction in comparison to the aromatic cycloaddition with the slightly more remote benzyl protecting groups. In order to take these benzyl groups out of the equation we turned to methoxy protecting groups, since these groups should be inert to the generated metal carbene, thus giving the targeted insertion reaction a higher probability. Diazocompound **12** was prepared for this purpose via a route similar to that used for **3** (Scheme 4). Exposure of this diazocompound to a catalytic amount of $Rh_2(OAc)_4$ in CH_2Cl_2 resulted in two distinct major products on TLC. Both NMR and MS analysis of the two compounds indicated them to be the two 'carbene dimers' **13** and **14** obtained in a close to 1:1 ratio. Again no products from C–H insertion reactions could be identified.



Scheme 4. *Reagents and conditions*: (a) diketene, NEt_3, THF, 62 h; (b) MsN_3, NEt_3, THF, 4 h; (c) LiOH, THF/H_2O, 4 h, 60% (3 steps); (d) Rh_2OAc_4, CH_2Cl_2, 5 h, 63%.

For glucose and galactose derivatives **3** and **9**, C–H insertion reactions apparently were disfavored relative to aromatic cycloadditions. This happened despite the fact that several factors seemed to favor a C–H insertion, e.g. into H–C(4) of **9**. A favorable factor for CH-insertion is the fact that the ring formed would be a 5-membered one. Also favorable is the fact that the insertion would take place into a tertiary C–H bond and that the carbon C(4) contains an activating oxygen substituent. The fact that no insertion was observed indicates that the geometrical constraints of the ring system disfavor the required geometries towards the transition state in favor of the aromatic cycloaddition. In the unrestrained **5**, the C–H insertion is more favorable than the aromatic cycloaddition. The balance may be a delicate one, considering also that C–H insertion did occur in a constrained furanose sugar leading to a 5-membered ring.[2b] For these reasons, alternative geometries should be explored for insertion, which need not be limited to C–H bonds but could also include the O–H or N–H bonds. The reaction with the glucose derivative **12**, giving the 'carbene dimers', indicates that this compound had no favorable intramolecular pathways available for reaction. This also explains why compound **3**, with the same orientation of the diazoacetate group as **12**, 'found' only the intramolecular cycloaddition involving the benzyl protecting groups. The aromatic cycloaddition product **4** provides an interesting entry into a class of tricyclic constrained carbohydrates with increased lipophilicity and will be further explored. The carbene dimer formation, as shown for **12**, may be an interesting reaction as well, if used intramolecularly,[11] in the construction of constrained carbohydrates by making bridges between sugar residues in an oligosaccharide.

Acknowledgements

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