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Tandem reduction–reductive alkylation of azido sugars

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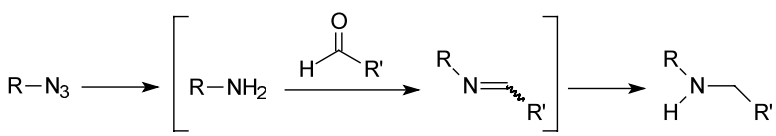
Abstract—Catalytic hydrogenation of azido sugars has been conducted in the presence of different aldehydes to bring about a tandem reduction–reductive alkylation sequence. The reaction sequence proceeds in generally high yields, and tolerates some benzyl and benzylidene protecting groups that are sensitive to hydrogenolysis. © 2002 Elsevier Science Ltd. All rights reserved.

Reductive alkylation of amines, or reductive amination of aldehydes and ketones, has been pursued extensively to prepare primary, secondary and tertiary amines.[1] There is an abundant selection of reagents to effect this transformation, including $NaBH_3(CN)$,[2] $NaBH(OAc)_3$,[3] $Zn(BH_4)_2$ and silica gel,[4] and others.[5] In recent times, much research in this area has focused on the development of tandem reaction strategies involving reductive alkylation or reductive amination. For example, reductive alkylation–cyclization has been used to prepare 2,3-diketopiperazines,[6] a double reductive amination has been used to prepare polyhydroxylated piperidine alkaloids,[7] and a triple reductive amination strategy has been reported in a route to indolizidine alkaloids.[8] Most recently, a tandem reduction–reductive amination has been disclosed with aromatic nitro compounds,[9] which involves initial reduction to the amines followed by an intramolecular reductive amination under conditions of catalytic hydrogenation. Catalytic hydrogenation also has been used in reductive alkylation of azido ketones or aldehydes, and this approach has been exploited in syntheses of piperidine alkaloids[10] and azasugars.[11] However, most of these reduction–reductive amination sequences have been limited to substrates where the reductive alkylation can be carried out in an intramolecular fashion.[12]

In conjunction with efforts to prepare new mannosamine derivatives,[13] we have investigated a tandem reduction–reductive alkylation based on an intermolecular reaction between an azide and an aldehyde. In this case, a successful tandem sequence would require initial reduction to the amine, subsequent imine formation, and final reduction of the imine to the secondary amine (Scheme 1). This strategy has proven to be an efficient approach to secondary amine derivatives of amino sugars.

To conduct this three-step process in a tandem fashion, several factors must be considered. Catalytic reduction of azides can be accomplished in many solvents, but because previous studies have shown that imine formation is faster in methanol than in other conventional solvents,[3] anhydrous methanol was selected as the solvent of choice for this sequence. A relatively large amount of palladium catalyst was employed based on a report that nonaromatic amines reduced the reactivity of palladium catalysts,[14] but only 1 equiv. of the aldehyde was employed to minimize the risk of over alkylation. To test these conditions with a representative sugar-derived azide, the carbohydrate **1**[15] was treated with different aldehydes in the presence of 10% Pd/C under typical conditions for catalytic hydrogenation (Table 1). With the aliphatic aldehydes employed, the reaction sequence proceeded very smoothly. For example, when compound **1** was treated with butanal (**2**) or cyclohexancarboxaldehyde (**4**), the secondary amines **3**



Scheme 1. Tandem reduction–reductive alkylation of azides.

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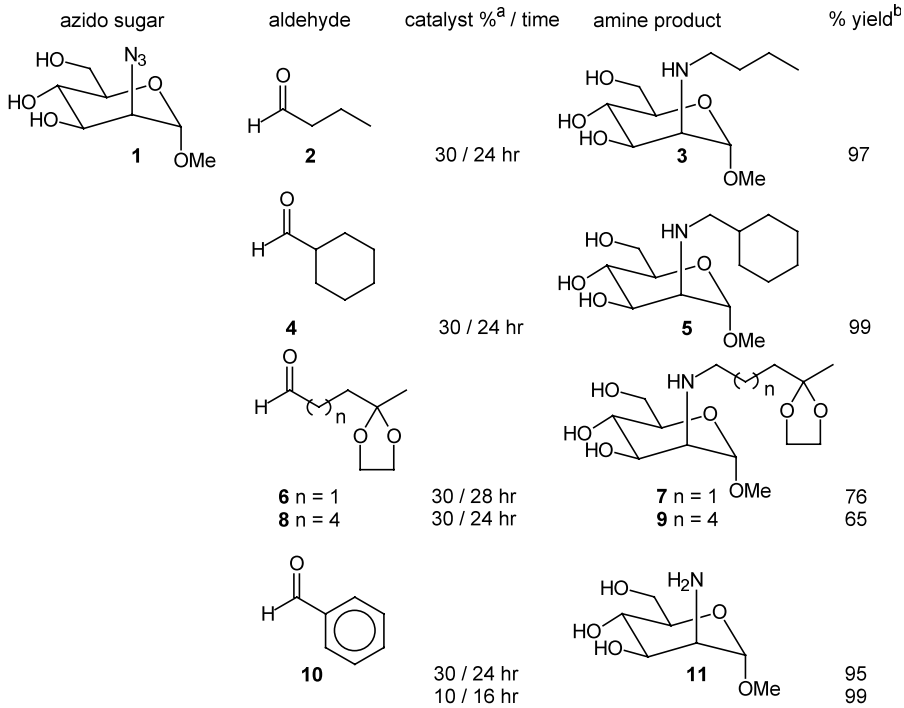
Table 1. Tandem reaction of sugar **1** with varied aldehydes



[a] Weight of catalyst (10% Pd/C) as a percentage of the weight of azide plus aldehyde.
[b] Isolated yield after column chromatography.

and **5** were isolated in nearly quantitative yield with no detectable formation of the corresponding tertiary amines. The ketal aldehydes **6** and **8** reacted to afford the expected ketals **7** and **9** in slightly lower yield, but again there was no trace of the tertiary amine. However, when the reaction was attempted with benzaldehyde (**10**), only the parent amine **11** was observed, along with benzyl alcohol.

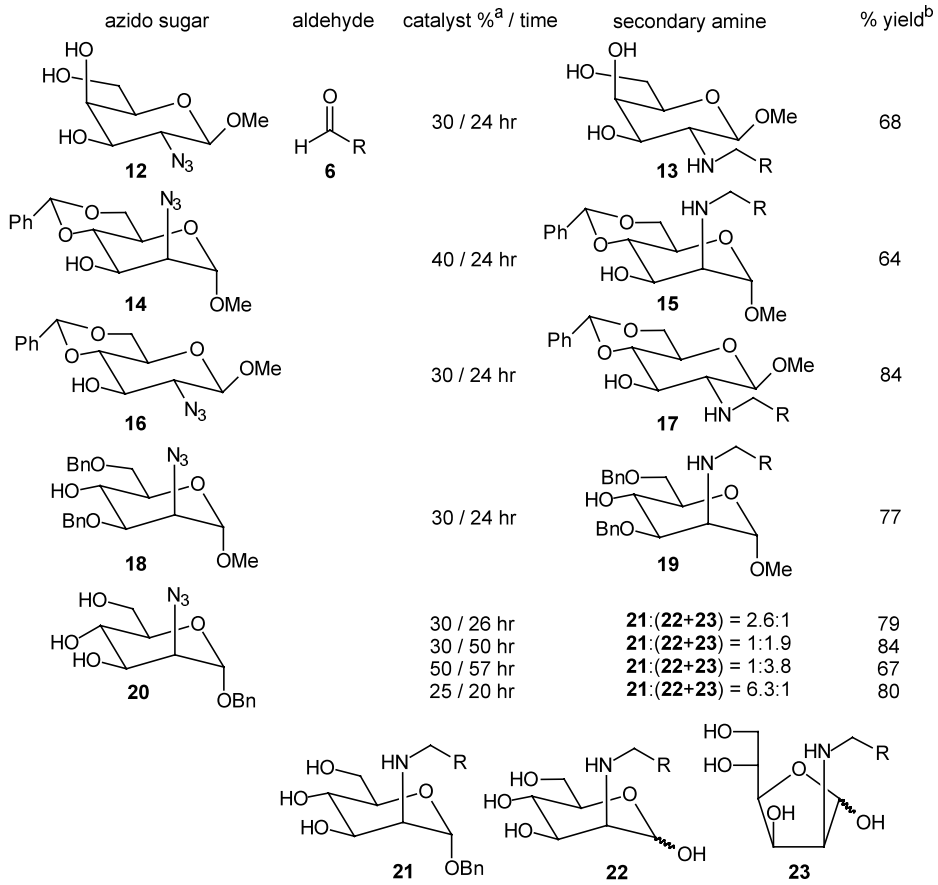
Both benzyl and benzylidene protecting groups are commonly used in the synthetic carbohydrate chemistry and they can be removed conveniently by hydrogenolysis.[16] To test the durability of some benzyl and benzylidene protecting groups to these conditions, a series of azido sugars (Table 2) was treated with aldehyde **6** under these reductive amination conditions to give a series of secondary amines. When the minimally protected sugar **12**[17] was subjected to the standard reactions conditions, the desired secondary amine **13** was isolated in 68% yield, a yield comparable to that observed for preparation of compound **7**. When the benzylidene protected azido sugars **14**[18] or **16**[19] were used as the substrate, the corresponding secondary amines **15** and **17** were obtained with no evidence of removal of the benzylidene functionality. This selectivity also holds true for benzyl ether protected azido sugar **18**,[20] which gave the corresponding secondary amine **19** in 77% yield without loss of the benzyl groups.

In all of the above cases, no cleavage of the benzyl or benzylidene groups could be detected. These results suggest that the amines formed in the reaction sequence may be involved in yet another process. Presumably the amine products lower the reactivity of the palladium catalyst[14] to levels such that cleavage of benzylidene and benzyl protecting groups is at least substantially slowed, and apparently completely prevented, even though reduction of the parent azides and the imine intermediates can still be accomplished.

In contrast to these results, when the benzyl glycoside **20**[21] was subjected to the standard reaction conditions the secondary amine **21**, in which the benzyl group was retained, was isolated in just 57% yield along with 22% of a mixture of compounds **22** and **23** in which the benzyl group had been cleaved. Interestingly, this free amino sugar exists in both the pyranose (**22**) and the furanose (**23**) forms.[22] When the reaction time was extended to a longer period, the deprotected sugar mixture (i.e. compounds **22** and **23**) was isolated as the major product. This demonstrates that the benzyl protecting group at the anomeric position is more susceptible to hydrogenolysis under these conditions than the benzyl ethers of compound **18**. In an attempt to fully remove the anomeric benzyl group of compound **20**, a larger quantity of palladium catalyst and prolonged reaction time were used. These conditions did double the ratio of the free sugars **22**/**23** to the benzyl mannoside **21** but did not result in improved yield. Finally, when lesser amounts of catalyst and time were employed, the product ratio favored the benzyl glycoside **21** by about 6:1.

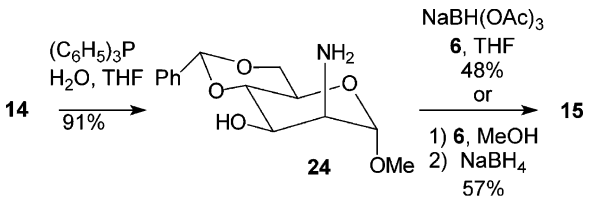
In order to compare this method with other commonly used reductive amination procedures,[3] the azido sugar

Table 2. Tandem reactions of varied sugars with aldehyde **6**



[a] Weight of catalyst (10% Pd/C) as a percentage of the weight of azide plus aldehyde.
[b] Isolated yield after column chromatography.

14 was reduced[23] to the corresponding amine **24**. When amine **24** and aldehyde **6** were subjected to direct reductive alkylation with $NaBH(OAc)_3$[3] or to a two-step procedure that involves formation of the imine followed by reduction with $NaBH_4$,[3] the secondary amine **15** was isolated in 48 and 57% yields, respectively.[24] Thus, the tandem reduction–reductive alkylation of this compound proceeds in higher yield and also avoids the need for purification of the intermediate amine.



In conclusion, we have developed a tandem reduction–reductive alkylation procedure for preparation of secondary amines directly from azido sugars. We have demonstrated that the process is viable with minimally protected sugars bearing several free hydroxyl groups, that benzylidene and benzyl protecting groups can survive these conditions, but that an anomeric benzyl group is more susceptible to hydrogenolysis. This new method gives better yields of the desired secondary amines than commonly used reductive amination protocols with a representative substrate, and the tandem approach also offers advantages in that the reactions are clean and easy to workup.[24] Thus, it is reasonable to believe that this methodology can be applied to achieve intermolecular reduction–reductive alkylation with a variety of other organic azides.

Acknowledgements

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24. A representative procedure for tandem reduction–reductive alkylation of azido sugars: methyl 2-deoxy-2-*N*-(4-ethylenedioxypentyl)-α-D-mannopyranoside (**7**). A mixture of compound **1**[15] (1.07 g, 4.90 mmol), aldehyde **6** (707 mg, 4.90 mmol) and 10% Pd/C (504 mg) was hydrogenated in MeOH (40 mL) under H_2 (40 psi) at rt for 27.5 h, and then filtered. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (7:1 $CHCl_3$:MeOH) to give compound **7** as a clear syrup (1.20 g, 76%): ^{1}H NMR (400 MHz, D_2O) δ 4.81 (d, $J=1.1$ Hz, 1H), 4.07–3.97 (m, 4H), 3.92 (dd, $J=9.4$, 4.7 Hz, 1H), 3.89–3.84 (m, 1H), 3.83–3.76 (m, 1H), 3.63–3.55 (m, 2H), 3.41 (s, 3H), 2.97 (dd, $J=4.7$, 1.4 Hz, 1H), 2.72 (dt, $J=11.8$, 7.4 Hz, 1H), 2.55 (dt, $J=11.8$, 7.4 Hz, 1H), 1.75–1.68 (m, 2H), 1.63–1.52 (m, 2H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, D_2O) δ 113.3, 101.6, 75.0, 72.5, 69.3, 67.1 (2C), 63.5, 63.5, 57.5, 50.8, 38.2, 26.0, 25.5; HRMS calcd for $C_{14}H_{28}NO_7$ $(M+H)^+$ 322.1866, found 322.1860.