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Henry condensations with 4,6-*O*-benzylidenylated and non-protected D-glucose and L-fucose via DBU-catalysis

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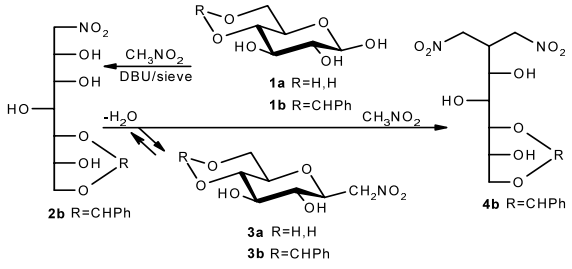
Abstract—Mechanistic intermediates, and thermodynamically favored side products, in the Henry condensations of partially protected and non-protected pyranoses with a free anomeric hemiacetal function with nitromethane in various solvents for the kinetically controlled syntheses of *C*-glycopyranosides in the presence of DBU/molecular sieve catalyst system were identified.

Carbohydrates play an important role in the biological activity of glycoconjugates such as glycolipids, blood-group antigens and complex glycoconjugates of plant, bacterial or viral origin.[1] A particular class of carbohydrate derivatives, *C*-glycoside carbohydrate analogs are important enzyme inhibitors.[2] Being structurally, chemically, and conformationally similar to *O*-glycosides[3] but acid- and enzymatically stable, aminomethyl *C*-glycosides are potentially more stable as mimetics and pseudo-substrates.[4] They are obtainable from nitromethyl *C*-glycosides.[4b]

One of the most common methods for the chain extension of carbohydrates is the Henry condensation of pentoses and hexoses with nitromethane in the presence of a strong base. In 1946 Sowden and Fisher condensed 4,6-*O*-benzylidene-D-glucose **1b** with nitromethane in the presence of methoxide to give acyclic D-heptitol **2b** and cyclic nitromethyl β-D-glucopyranoside **3b** in 21 and 5% yield, respectively.[5] Later, Petrus et al. improved the total yields of unprotected nitromethyl D-hexopyranosides, but their approach is lengthy and complicated, requires careful workup, with adjustment of pH, and produces isomeric mixtures.[6a] Strong bases (HO^-, MeO^-) in these procedures in protic solvents[5] lead to acyclic compounds (i.e. **2b**, Scheme 1). Their hot dehydration[6b] ($\Delta S>0$; $\Delta G=\Delta H-T\Delta S$) gives cyclic forms, reverting only very slowly to acyclics, at low temperatures. Presumably, acyclics, having more hydroxyl groups, are stabilized by solvation in protic solvents.

We had synthesized[7] **directly** cyclic compounds in aprotic solvents with a highly active bifunctional[8a] catalyst 2-hydroxypyridine[8b] and DBU/molecular sieve[7a] with an improved[7b] yield of 77%. We avoided protic solvents in view of the quoted (Scheme 3) p*K*a of DBU, which would provide just another way of creating RO^-, in ROH. The cyclic **3b** was produced in a single step along with two minor byproducts[7a] **2b** and **4b**.



Scheme 1.

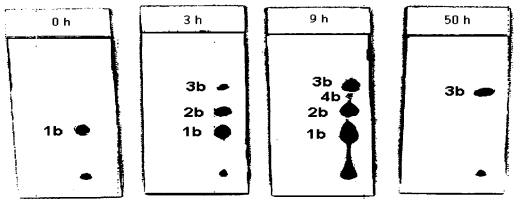


Figure 1. TLC analysis (SiO_2; 6:1 $CHCl_3$:MeOH) of reaction of 4,6-*O*-benzylidene-D-glucopyranose with CH_3NO_2 and DBU/molecular sieve, in THF (Due to weaker spotting, **4b** is not visible on the 50 h plate).

Keywords: nitromethane; *C*-glycoside; DBU.

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The actual catalytic molecule, whether it was 2-HP, a known 1,3-proton transfer catalyst for pyranose ring opening in benzene,[8b] the anionic form of 2-HP, DBU, or the protonated form of DBU, had not been unequivocally determined. The effects of aprotic solvents and of 4,6-*O*-acetalation with respect to the system's catalytic efficiency had yet to be clarified. Also, this condensation procedure had not been extended to simple sugars such as L-fucose. Since few 4,6-*O*-alkylidene glycopyranoses are easily accessible, advantages of such extensions had not been fully realized.

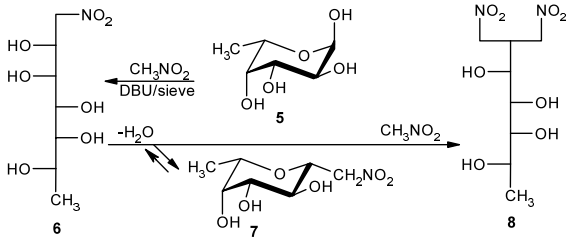
We reinvestigated our original condensation[7] of nitromethane with 4,6-*O*-benzylidene-D-glucopyranose **1b** to nitromethyl 4,6-*O*-benzylidene β-D-glucopyranoside **3b** and discovered that 2-HP was unnecessary. A time study, with careful TLC analysis and flash chromatography of the reaction mixture with DBU and molecular sieve revealed sequential products, which are conveniently explained as outlined in the mechanistically simplified Scheme 1.

The condensation progressed similarly in THF (Fig. 1)[9] and dioxane, with 4,6-*O*-benzylidene-D-glucopyranose via the acyclic 5,7-*O*-benzylidene-1-deoxy-1-nitro-D-*glycero*-D-*gulo*-heptitol **2b**, which subsequently changed into nitromethyl β-D-glucopyranoside **3b**. The former was observed accumulating before being further converted during at least 50 h at room temperature to the cyclic product **3b**, along with some 5,7-*O*-benzylidene-1,2-dideoxy-1-nitro-2-nitromethyl-D-glucoheptitol **4b**, in yields similar to those already reported.[7] In THF or dioxane, accumulation of the final acyclic product **4b** was dependent on temperature, time, and solvent: less decomposition was observed with dioxane. In these condensations, we could not determine if the presence of 2-HP had any effect at all, at any stage of the reaction. In any case, the first acyclic heptitol **2b** and the desired cyclic **3b** were kinetically controlled intermediates, which, given enough time, were transformed into the 'thermodynamic' product **4b**, by a still slower overall rate. Compound **2b**,[5] **3a**,[6] **3b**, and **4b**[7] have already been fully characterized.

When similar conditions were employed for unprotected D-glucose **1a**, there was no reaction for prolonged periods of time. Heating only resulted in almost complete decomposition. This was expected since unprotected sugars are typically not very soluble in THF or dioxane. But when acetonitrile, pyridine or a mixture of these was used as the solvent and the reaction temperature kept at 50°C, the condensations were fairly clean.[10] The condensation progressed to completion within one day, and only nitromethyl β-D-glucopyranoside **3a** was detected and isolated when 5:1 acetonitrile/pyridine (38% yield) or pyridine (57% yield) were used as solvents (Scheme 1). For completion and maximal yield, a stoichiometric amount of DBU was needed.

Condensations with L-fucose[10] were monitored by TLC and flash chromatography, and gave sequential products as outlined in Scheme 2, summarized in Table 1. Under procedure **A** and **B**, within 12 h more than half of the starting L-fucose **5** was converted into its corresponding 1,6-dideoxy-1-nitro-L-*glycero*-D-*manno*-heptitol **6**. By the end of day 3, most of L-fucose had been transformed into the acyclic heptitol **6**, and the subsequent conversion into cyclic nitromethyl β-L-fucopyranoside **7** was followed for another 5 days, during which time a significant portion of the desired cyclic product had also been slowly converted into 1,1,6-trideoxy-1-nitro-2-nitromethyl-L-galactoheptitol **8**. Thus, the maximal yield for desired cyclic product **7** required minimizing decomposition and the yields of **6** and **8**. The best system discovered is shown for procedure **D** (Table 1). Under this condition, only **7** was isolated as the product. In addition, there were decomposition products that did not move on the column or on TLC.

For the condensation of 4,6-*O*-benzylidene-D-glucopyranose, its slow dissolution rate in THF and acetonitrile was likely rate-determining step. Acyclic intermediate **2b** was observed accumulating, but most of the starting



Scheme 2.

Table 1. Reaction parameters and yields for Henry condensations of **5**[10]

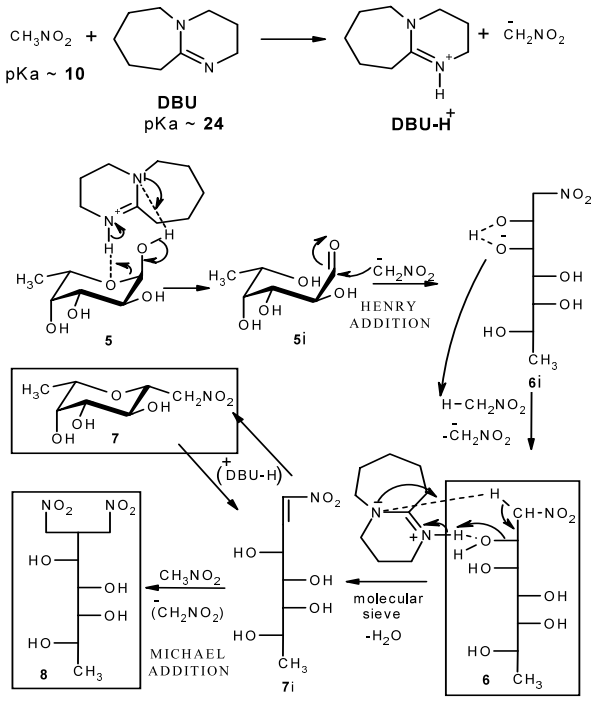
Procedure #	Solvent	Ratio of **5**:DBU:2-HP	%/Yield[a] **6**:**7**:**8**	*t*[b]	*T*[c] (°C)
A	THF	1.0:1.2:0.5	5:35:11	9	70
B	THF	1.0:1.2:0	5:51:5	9	70
C	Dioxane	1.0:1.2:0.5	0:49:8	1.5	50
D	Dioxane	1.0:1.2:0	0:62:0	1.5	50
E	MeCN	1.0:1.2:0	0:30:25	1	25
F	Pyridine	1.0:1.2:0	0:27:31	1	25
G	DMF	1.0:1.2:0	0:5:50	0.5	25

[a] Isolated yields.
[b] Time in days.
[c] Temperature.

1b also remained unconverted. In pyridine, complete dissolution of non-protected D-glucose (**1a**, Scheme 1) was observed within a few minutes. These results suggest that solubility might be the most important factor that affected Henry condensations of unprotected sugars. Instructive in this respect were the condensations of L-fucose under procedure **A** and **B** (Table 1): Complete dissolution of L-fucose occurred in about 5 h, after which viscosity of the reaction mixture increased and acyclic heptitol **6** was precipitating. This precipitation from THF explained why conversion of **6** into **7** was slow. When more polar solvents were employed to increase the solubility of acyclic heptitol to accelerate this conversion, another difficulty appeared: The ratios of products significantly shifted all the way towards the thermodynamically favored 1,1,6-trideoxy-1-nitro-2-nitromethyl-L-galactoheptitol **8** (as seen in procedure **E** to **G**). This shift was also observed when condensations were performed under procedure **A** and **C** for a prolonged period of time, in the presence of 2-HP, although not as efficiently.

A possible mechanism of these Henry condensations must account for the isolated intermediates and products outlined in Schemes 1 and 2. The most probable mechanism, for the example of L-fucose, is illustrated in Scheme 3 (mechanistic intermediates are labeled 'i'). This scheme accounts for all facts known to us. The condensations required a 2-hydroxyl proton for the Henry adduct alkoxide. 2,3,4-Protected glycosides that lack the required stabilizations failed to undergo Henry condensation with our system.[7]

Several aspects of the described condensations make a 'classical' base catalyzed mechanism unlikely. In contrast to the Fischer–Sowden scheme, we could not find by NMR or TLC any evidence for the 2-epimers of **6** or **2b**. Also, replacement of DBU by bases not capable of forming bifunctional catalysts such as TEA, Hunig's base, DABCO or Proton-Sponge resulted in no reaction. In the presence of excess nitromethane ($pK_a = 10$), DBU ($pK_A = 24$) exists predominantly in its protonated form together with nitromethyl anion, which has only the basicity of phenolate. DBU-H$^+$ is an even weaker base, but it may complex with L-fucose to catalyze the glycosidic ring opening and formation of its aldehyde form (**5i**) in one step. After Henry addition of nitromethyl anion and stabilization of the resultant alkoxide **6i** by an adjacent 2-hydroxyl proton, formation of the intermediate acyclic heptitol **6**, DBU-H$^+$ could catalyze its dehydration with assistance of molecular sieve into intermediate **7i** and subsequent cyclization into **7**. From this perspective, under procedure **A** and **C**, addition of 2-HP might just mean a better 1,3-proton transfer, which also skewed the reaction towards **7i** and allowed for the increased addition of another mole of nitromethane into acyclic **8**. So, not only was 2-HP not required for the initial ring opening in our Henry condensations, it actually had an adverse effect on the yield of the desired cyclic product (procedure **A** and **C**, Table 1).



Scheme 3.

The conversion **7** to **7i** is formally analogous to **5** to **5i**. DBU-H$^+$ may also serve as a dehydration catalyst (**6**→**7i**). The reverse reaction (**7i**→**6**) is trimolecular, and in presence of molecular sieves irreversible. Reaction (**5i**→**5**) would be fast, but is omitted for clarity, since **5i** is depleted as shown. The dehydration, and the C–C bond forming reactions (**5i**→**6**; **7i**→**8**) provide the driving force.

It is also very likely that solvents play an important role in the stabilization of alkoxides **6i** (Scheme 3): The most polar solvent, DMF, showed the fastest reaction. In good solvents, where solubility was not a problem, with molecular sieve, dehydration of acyclic heptitol **6** into nitroalkene **7**i and cyclization into the desired cyclic nitromethyl β-L-fucopyranoside **7** occurred readily. Good solvents, such as acetonitrile, pyridine and DMF (procedure **E** to **G**, Table 1), may have skewed the reaction towards the intermediate nitroalkene **7i**, which then reacted with another mole of nitromethane to form almost exclusively the thermodynamically favored 1,1,6-trideoxy-1-nitro-2-nitromethyl-L-galactoheptitol **8**. High reaction rates are generally associated with low selectivity and thermodynamic control of products. The discovery of the acyclic **8** as thermodynamic end product with excess $MeNO_2$ at low temperatures was actually to be expected for reasons discussed in the introduction of this article.

The actual mechanism is probably governed by a combination of several factors. In any case, some intermediates and sequences have been established, and the conditions required for kinetically controlled synthesis of the desired cyclic products from 4,6-*O*-benzylidene D-glucose, unprotected D-glucose and L-fucose have been determined. This methodology should be extendable to other sugars.

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9. **Procedure**: 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU; 1.4 ml, 9.3 mmol) was slowly added to a mixture of 4,6-*O*-benzylidene-D-glucopyranose **1b** (5.0 g, 19.0 mmol), $MeNO_2$ (10 ml, 190 mmol), THF (50 ml), and molecular sieve (3 Å, 10 g). The slurry was stirred under N_2 at rt for 50 h and was filtered. The filtrate was concd in vacuo. The residual oil was chromatographed (SiO_2, 8:1:1 CH_2Cl_2/EtOAc/Et_2O). Fractions containing the slowest product at 375–475 ml were collected and were concd in vacuo. The residue was recrystallized from THF to give **2b**: 0.064 g, 0.2 mmol (1.1%); mp 164–165°C. Fractions at 75–275 ml were concd in vacuo and were recrystallized from THF/$(i\text{Pr})_2O$ to give **3b**: 3.6 g, 11.6 mmol (61%); mp 210–212°C. Fractions at 300–375 ml were concd in vacuo and were recrystallized from THF/$(i\text{Pr})_2O$ to give **4b**: 0.15 g, 0.39 mmol (2.1%); mp 124–126°C.
10. **General procedure**. DBU (1.1 ml, 7.3 mmol) was slowly added to a mixture of L-fucose **5** (1.0 g, 6.1 mmol) with (procedure **A** and **C**, Table 1) or without (procedure **B**, **D** to **G**, Table 1) 2-HP (0.6 g, 6.1 mmol), $MeNO_2$ (10 ml, 190 mmol), solvent (50 ml), and molecular sieve (3 Å, 5 g). The slurry was stirred under N_2 at 25–70°C for 0.5 to 9 days and was filtered. The filtrate was concd in vacuo. The residual oil was chromatographed (SiO_2, EtOAc).
Fractions containing the slowest product at 725–875 ml were collected and were concd in vacuo. The residual crystals were recrystallized from EtOAc/THF to give **6**: 0.07 g, 0.0003 mol (5.0%); mp 138°C; $[\alpha]_D^{20}$ +10.0°, $c=0.7$ (MeOH); TLC system (EtOAc): R_f 0.13; IR 3200–3400, 2940 (OH), 1550, 1650 (NO_2); ^{1}H NMR (CD_3OD) 4.88 (dd, CH^aNO_2), 4.48 (dd, CH^bNO_2), 4.34–4.41 (m, $J_{1,2}=8.4$ Hz, H^1), 3.76 (dd, H^2), 3.86 (dd, H^3), 3.41 (dd, H^4), 4.06 (dq, H^5), 1.24 (d, CH_3); ^{13}C NMR (CD_3OD) 80.8 (CH_2NO_2), 74.5 (C^1), 67.5 (C^2), 70.1 (C^3), 72.2 (C^4), 70.5 (C^5), 20.0 (CH_3); MS-ESI$^+$ (in MeOH ionization) m/z 250.2 $[5M+4Na+MeOH]^{5+}$, 291.0 $[7M+3Na+MeOH+3H]^{6+}$. Anal. calcd for $C_7H_{15}O_7N$ (225.26): C, 37.32; H, 6.71; N, 6.22. Found; C, 36.83; H, 6.69; N, 6.12.
Fractions containing the major product at 425–600 ml of procedure **A** and **B** were collected and were concd in vacuo. The residual crystals were recrystallized from THF/$(i\text{Pr})_2O$ to give **7**: [0.44 g, 2.1 mmol (35%)] (**A**); and [0.64 g, 3.1 mmol (51%)] (**B**); mp 182°C; $[\alpha]_D^{20}$ −26.0°, $c=1$ (MeOH); TLC system (EtOAc): R_f 0.18; IR 3200–3400, 2940 (OH), 1550, 1650 (NO_2); ^{1}H NMR (CD_3OD) 4.82 (dd, CH^aNO_2), 4.49 (dd, CH^bNO_2), 3.90 (dt, $J_{1,2}=9.3$ Hz, H^1), 3.44 (dd, H^2), 3.50 (dd, H^3), 3.63 (dd, H^4), 3.90 (dq, H^5), 1.20 (d, CH_3); ^{13}C NMR (CD_3OD) 78.4 (CH_2NO_2), 78.2 (C^1), 69.2 (C^2), 73.4 (C^3), 76.2 (C^4), 75.7 (C^5), 16.9 (CH_3); MS-ESI$^+$ (in MeOH ionization) m/z 230.0 $[M+Na]^+$. Anal. calcd for $C_7H_{13}O_6N$ (207.18): C, 40.58; H, 6.32; N, 6.76. Found; C, 40.40; H, 6.32; N, 6.69.
Procedure C: **procedure A** was modified by substituting dioxane (50 ml) for THF and decreasing the reaction time to 36 h. Fractions containing the major product at 400–700 ml were collected, and were concd in vacuo. The residue was recrystallized to give **7**: 0.62 g, 3.1 mmol (49%).
Procedure D–G: **procedure B** was modified by substituting 50 ml of either dioxane (**D**), MeCN (**E**), pyr (**F**) or DMF (**G**) for THF and changing the reaction time to 36, 24, 24, and 12 h, respectively. Fractions containing the major product at about 400–700 ml were collected, were concd in vacuo, and were recrystallized to give **7** in the following yields: [0.78 g, 3.8 mmol (62%)] (**D**); [0.38 g, 1.8 mmol (30%)] (**E**); [0.38 g, 1.6 mmol (27%)] (**F**); and [0.62 g, 0.3 mmol (5.0%)] (**F**).
Fractions containing the fastest product at about 200–300 ml of procedures **A**, **B**, **C**, **E**, **F**, **G** were collected, and were concd in vacuo. The residue was recrystallized from $(i\text{Pr})_2O$ to give **8** in the following yields: [0.18 g, 0.67 mmol (11%)] (**A**); [0.08 g, 0.31 mmol (5.0%)] (**B**); [0.13 g, 0.49 mmol (8.0%)] (**C**); [0.41 g, 1.5 mmol (25%)] (**E**); [0.51 g, 1.9 mmol (31%)] (**F**); and [0.82 g, 3.0 mmol (50%)] (**G**); mp 138°C; $[\alpha]_D^{20}$ +7.5°, $c=1$ (MeOH); TLC system (*A*): R_f 0.30; IR 3200–3400, 2940 (OH), 1550, 1650 (NO_2); ^{1}H NMR (CD_3OD) 4.96 (dd, CH^aNO_2), 4.80 (dd, $CH^{a'}NO_2$), 4.69 (ddd, CH^bNO_2, $CH^{b'}NO_2$), 3.31 (m, $J_{1,2}=6.6$ Hz, H^1), 4.01 (dd, H^2), 3.60 (dd, H^3), 3.37 (dd, H^4), 4.06 (dq, H^5), 1.23 (d, CH_3); ^{13}C NMR (CD_3OD) 93.1 (CH_2NO_2), 92.4 (CH_2NO_2), 58.5 (C^1), 89.6 (C^2), 84.6 (C^3), 92.1 (C^4), 87.0 (C^5), 37.5 (CH_3); MS-ESI$^+$ (in MeOH ionization) m/z 248.0 $[4M+5MeOH+5H]^{5+}$. Anal. calcd for $C_8H_{16}O_8N_2$ (268.22): C, 35.82; H, 6.01; N, 10.44. Found; C, 35.27; H, 6.15; N, 10.14.