Solvent-Free and Stereoselective Synthesis of *C*-Glycosides by Michael-Type Addition of Enamino Esters to 2-Nitro-D-glucal

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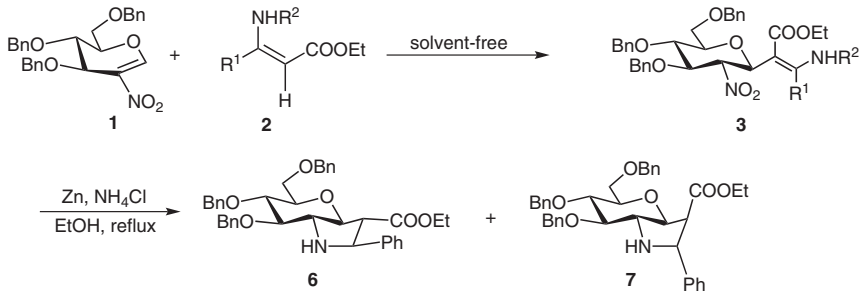
Abstract: Michael-type addition of enamino esters to 3,4,6-tri-*O*-benzyl-2-nitro-D-glucal under solvent-free conditions formed *C*-glycosides in excellent yields with high stereoselectivity. Reduction of the nitro group afforded the corresponding bicyclic 2-amino *C*-glycosides.

Key words: solvent-free, *C*-glycosides, Michael-type addition

C-Glycosides, either synthetic or naturally occurring, are an important class of bioactive compounds.[1] In contrast to their O-analogues, *C*-glycosides are less vulnerable to enzymatic and chemical hydrolyses, which has led to significant interest in their viability as drug candidates and enzyme inhibitors. The synthesis of *C*-glycosides has hence attracted much attention from synthetic organic chemists and methods for the formation of *C*-glycosides are well documented in the literature.[2] The synthetic strategy for *C*-glycosides usually involves the construction of the anomeric C–C bond using the nucleophilic, electrophilic, or radical character of the anomeric center, and concerted reactions have also been employed for *C*-glycosidation.[3] Electrophilic reactions were probably most widely applied to C-glycosidation and commonly used C-nucleophiles include organometallics, cyanides, *C*-silylate compounds, alkenes, and activated aromatic and β-dicarbonyl compounds. Only a few applications of enamino esters as nucleophiles for *C*-glycosidation have been reported in the literature.[4] Due to their easy preparation, considerable stability, and bisnucleophility, enamino esters are a remarkable class of synthetic intermediates with diverse reactive properties, and they have been widely used in the synthesis of alicyclic, aromatic and heterocyclic compounds.[5] Hence, it would be significant not only in carbohydrate chemistry but also in synthetic organic chemistry to develop a convenient, efficient and practical method for the *C*-glycosidation of enamino esters.

Solvent-free reactions, due to the advantages of less pollution, lower expense, and easier procedures, have attracted considerable attention from synthetic organic chemists.[6] However, the application of solvent-free reactions in carbohydrate chemistry has been limited.[7] Herein, we report a solvent-free *C*-glycosidation method by using Michael-type addition of enamino esters to 3,4,6-tri-*O*-benzyl-2-nitro-D-glucal (**1**).[8]

The 2-nitro-D-glucal **1** was prepared according to a reported method.[9] Enamino ester **2d** was chosen as a model substrate in the test reactions with **1** (Scheme 1; R^1 = Ph, R^2 = Bn). Considering that the Michael addition reactions were usually performed with the aid of a base,[10] the reactions between **1** and **2d** were initially carried out in the presence of various bases, such as: NaH, *t*-BuOK, CH_3ONa, DBU, Et_3N or DMAP, and in various solvents (CH_2Cl_2, MeCN, THF, 1,4-dioxane, toluene or DMF). Unfortunately, either no reaction occurred or complex mixtures of products were generated under such reaction conditions. Subsequently, in order to optimize the reaction conditions, the influence of concentration on the outcome of the glycosidation was examined, and the reaction between **1** and **2d** was attempted in concentrations ranging from 0.05 M to solvent-free conditions. To our de-



Scheme 1 Solvent-free and stereoselective *C*-glycosidation by Michael-type addition of enamino esters to 2-nitro-D-glucal

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light, the reaction proceeded smoothly to give *C*-glycoside **3d** under solvent-free conditions. The appropriate temperature for the reaction, in terms both of yield and reaction time, was found to be 110 °C.[11] The reaction between a variety of enamino esters[12] **2a–k** and **1** were then attempted (Table 1). All reactions were complete within 5–8 hours and resulted in the formation of the desired *C*-glycosides **3a–k** in good yield (85–94%) with excellent β-stereoselectivity. The reactions of the enamino esters derived from ethyl acetoacetate (**2i–k**) with **1** should be performed at temperatures below 95 °C (Table 1, entries 9, 10, and 11) to avoid low yields. Although both β-C- and N-positions of enamino esters can act as nucleophilic centers and either could, in principle, be involved in the reactions with **1**, no *N*-glycoside was detected. Therefore, the reactions between **1** and **2** proceeded smoothly with excellent regio- and stereoselectivity. The presence of a nitro group at C-2 seemed to allow anchimeric assistance and consequently orientated the glycosylation in the direction of the β-anomer.

The configurations of *C*-glycosides were determined on the basis of their spectroscopic properties. For example, in the ^{1}H NMR spectra of **3d**, the anomeric hydrogen signal appeared as a doublet with $J_{1',2'} = 9.7$ Hz. Similarly, the H-2′ signal appeared as a triplet with $J_1 = J_2 = 9.7$ Hz. This clearly indicated a *trans* relationship between H-1′ and H-2′, and between H-2′ and H-3′. The structure assignment was also supported by an NOE experiment that indicated strong interactions between H-1′ and H-3′/H-5′ and between H-2′ and H-4′. It was inferred that H-1′ and H-3′/H-5′ were on the same side, whereas H-2′ and H-4′ were on the other side. The X-ray single crystal analyses of **3d** (Figure 1) and **3i** (Figure 2) unambiguously confirmed these assignments.[13]

Subsequently, we focused our attention on the *C*-glycosidation of heterocyclic enamines **4** (Table 2). The solvent-free reactions of heterocyclic enamino esters **4a** and **4b**[14] were conducted at 85 °C and were complete within 30 minutes, whereas the reactions of nitro-substituted heterocyclic enamines **4c** and **4d**[15] required longer reaction times and did not go to completion. The conversion ratio was not improved by addition of a base; on the contrary, the yields decreased dramatically (20–25%), due to the decomposition of 2-nitroglucal **1**. *C*-Glycosidation of het-

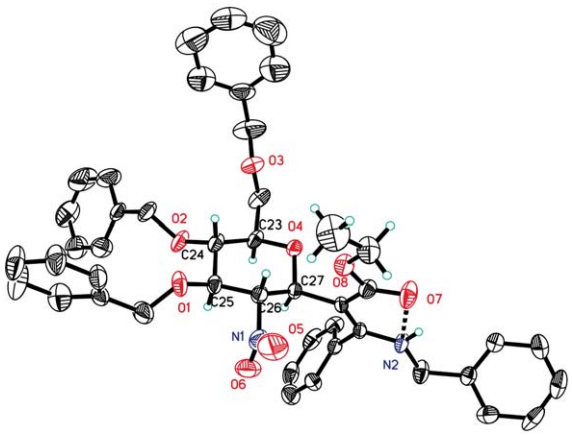
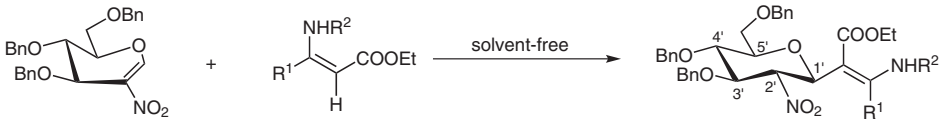


Figure 1 X-ray crystal structure of **3d**; partial hydrogen atoms bonded to carbon atoms have been omitted for clarity. The intramolecular hydrogen bond is indicated by a dashed line.

Table 1 Michael-Type Addition of Enamino Esters to 2-Nitro-D-glucal



Entry	Enamino ester	R^1	R^2	Temp (°C)	Time (h)	Yield (%)[a]
1	**2a**	Ph	H	110	8	85
2	**2b**	Ph	Me	110	6	87
3	**2c**	Ph	Ph	110	5	90
4	**2d**	Ph	Bn	110	5	94
5	**2e**	Ph	*n*-Pr	110	7	88
6	**2f**	Ph	*i*-Pr	110	5	92
7	**2g**	Ph	$CH_2CH{=}CH_2$	110	8	92
8	**2h**	Ph	CH_2CO_2Et	110	8	91
9	**2i**	Me	H	95	6	91
10	**2j**	Me	$CH_2CH{=}CH_2$	95	5	93
11	**2k**	Me	Bn	95	3	94

[a] Combined isolated yields after column chromatography.

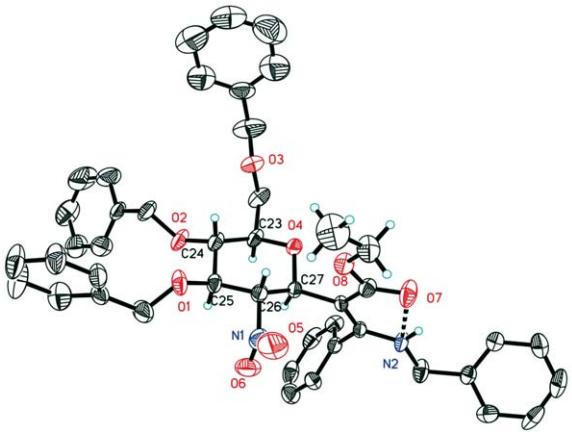


Figure 2 X-ray crystal structure of **3i**; partial hydrogen atoms bonded to carbon atoms have been omitted for clarity. The intramolecular hydrogen bond is indicated by a dashed line.

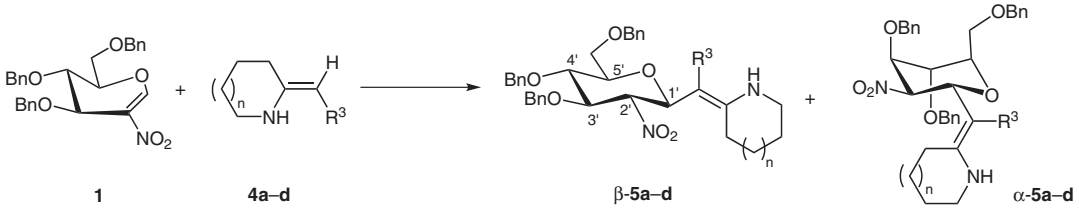
erocyclic enamino esters could proceed when refluxing in MeCN, albeit in lower yields. Because 2-nitroglucal **1** did not react completely (Table 2, entries 2 and 5), a catalytic amount of Et_3N was added to solve this problem (Table 2, entries 3 and 6). For six-membered heterocyclic enamines, only the β-anomer was obtained, whereas five-membered enamines afforded a mixture of two anomers. The results indicated that compounds with six-membered rings showed better stereoselectivity than those with five-membered rings.

The configurations of the *C*-glycosides were determined by analysis of their ^{1}H NMR and NOE spectra. For the α-anomer, the H-1′ signal appeared as a doublet with $J_{1',2'} = 9.8$ Hz, indicating a *trans* arrangement for H-1′ and H-2′; while the H-2′ signal appeared as a double doublet with $J_{2',3'} = 3.7$ Hz, indicating axial/equatorial arrangement for H-2′ and H-3′ and a $^1C_4$ conformation for **5a**-. This structural assignment was also supported by an NOE experiment, which demonstrated a strong interaction between H-1′ and H-6′.

The presence of a nitro group at C-2′ has several advantages; in particular, it would provide access to various 2-amino-*C*-glycosides,[16] which are important components of many glycoproteins that are attractive targets for the design of C-linked carbohydrate mimetics.[17] Accordingly, we then attempted the reduction of the nitro group. A variety of reagents and conditions for reduction of the nitro groups[18] were screened, including Raney Ni, Zn/Ac_2O and Zn/AcOH, but all these conditions led to unidentifiable mixtures of products. Fortunately, reduction of compound **3** with four equivalents of zinc dust and four equivalents of NH_4Cl in ethanol proved to be a relatively clean reaction, resulting in the formation of the unexpected bicyclic compounds **6** and **7** in good yields. Bicyclic compounds **6** and **7** were clearly formed through a sequence of reactions, i.e., reduction of the nitro group, followed by subsequent intramolecular cyclization along with the elimination of the amino group of the aglycon.

The ratio of products **6** and **7** ranged between 3:1 to 1.2:1 (Table 3); the configurations of the products were determined by ^{1}H NMR and NOE experiments. For compound **6**, the H-3 signal appeared at δ = 3.18 ppm as a double doublet with $J_1 = 9.8$ Hz and $J_2 = 8.2$ Hz, and the H-7a signal appeared at δ = 3.32 ppm as a triplet with $J_1 = J_2 = 9.2$ Hz. NOE experiments showed interactions between H-3a and H-2/H-5/H-7 and between H-7a and

Table 2 Michael-Type Addition of Heterocyclic Enamines to 2-Nitro-D-glucal

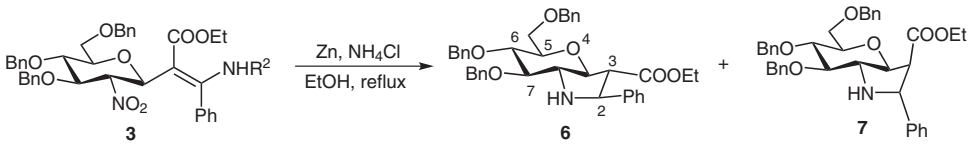


1 **4a–d** β-**5a–d** α-**5a–d**

Entry	**4**	n, R^3	Solvent	Temp (°C)	Additive	Recovered **1** (%)	Time (h)	Yield (%)	β/α
1	**4a**	0, CO_2Et	–	85	–	–	0.5	96[a]	98:2[b]
2	**4a**	0, CO_2Et	MeCN	reflux	–	10	5	74[a]	90:10[b]
3	**4a**	0, CO_2Et	MeCN	reflux	Et_3N	–	5	89[a]	90:10[b]
4	**4b**	1, CO_2Et	–	85	–	–	0.5	94	1:0
5	**4b**	1, CO_2Et	MeCN	reflux	–	15	8	70	1:0
6	**4b**	1, CO_2Et	MeCN	reflux	Et_3N	–	8	84	1:0
7	**4c**	0, NO_2	–	85	–	7	4	86[a]	93:7[c]
8	**4d**	1, NO_2	–	85	–	9	6	79	1:0

[a] Combined isolated yield after column chromatography.
[b] Ratio was determined from the isolated pure diastereomers.
[c] Ratio was determined by integration of the H-2′ signal in the ^{1}H NMR spectra (300 MHz).

Table 3 Reduction of 2-Nitro-*C*-glycosides



Entry	2-Nitro-*C*-glycoside	R^2	Time (h)	Yield (%)[a]	Ratio **6**/**7**[b]
1	**3a**	H	0.5	82	1.2:1
2	**3d**	Bn	0.5	87	3:1
3	**3e**	*n*-Pr	0.5	83	1.6:1
4	**3h**	CH_2CO_2Et	0.5	85	2:1

[a] Combined isolated yield after column chromatography.
[b] The ratio of **6** and **7** was determined by the isolation of pure diastereomers.

H-3/H-6, which indicated a *trans* relationship between H-2/H-3, H-3/H-3a and H-3a/H-7a. The H-3 signal of compound **7** appeared at δ = 2.91 ppm as a double doublet with $J_{3,2}$ = 8.9 Hz and $J_{3,3a}$ = 3.0 Hz, and the H-7a signal appeared at δ = 3.24 ppm as a triplet with $J_1 = J_2$ = 9.2 Hz. The *trans* relationship between H-2/H-3 and H-7a/H-3a and the *cis* relationship between H-3/H-3a could be observed from an NOE experiment (Figure 3).

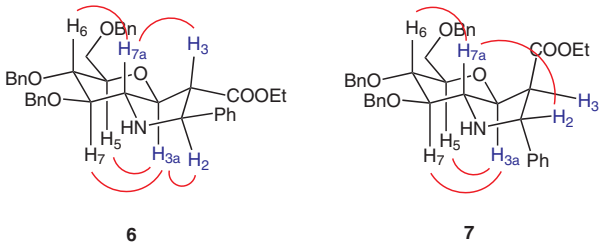


Figure 3 Key NOE correlations for bicyclic compounds **6** and **7**

In conclusion, an efficient, solvent-free *C*-glycosidation method has been developed based on the Michael-type addition of enamino esters to 3,4,6-tri-*O*-benzyl-2-nitro-D-glucal, which results in the formation of the desired *C*-glycosides in good yields and with excellent regio- and stereoselectivity. Reduction of the nitro group gave access to novel bicyclic 2-amino *C*-glycosides that are potentially useful as bioactive compounds, such as inhibitors of glycosidases.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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