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Passerini and Ugi Reactions of Anomeric Glucosyl Isonitriles

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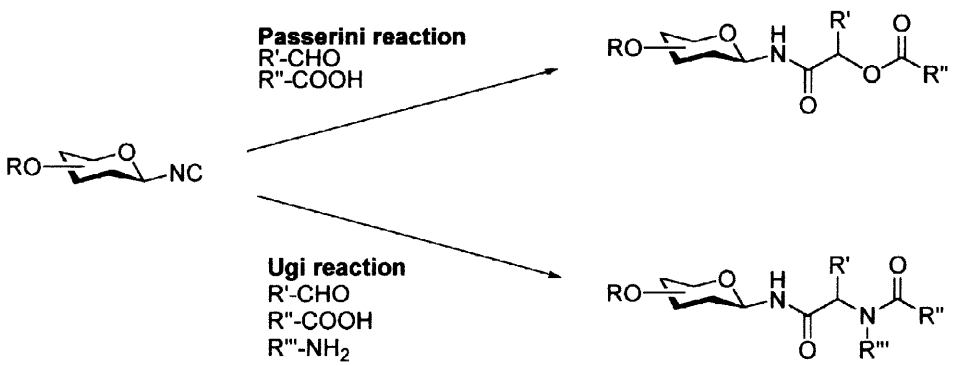
Abstract: Acetyl and benzyl protected β-D-glucopyranosyl isonitriles were treated with various aldehydes and acetic acid to give the corresponding Passerini reaction products and with *i*-butanal, carboxylic acids and amines to give the corresponding Ugi reaction products, respectively. No significant diastereoselectivity was observed for both reactions.

Although isonitriles, in general, have found wide applications as substrates and reagents in organic synthesis, the chemistry of anomeric glycosyl isonitriles - the first fully characterized examples were described by Descotes[1] and Zwikker[2] - has been examined only sporadeously yet.[3] In particular, Passerini and Ugi reactions[4] which are, so to speak, the realm of isonitrile chemistry have not been applied to anomeric glycosyl isonitriles so far.[5]

As part of a project toward the synthesis of combinatorial libraries of glycopeptides we therefore tested the potential of acetyl and benzyl protected anomeric glucosyl isonitriles in Passerini and Ugi reactions (Scheme 1). Applications of Ugi reactions for the combinatorial synthesis of peptide-like libraries either in solution or on a solid support are well established.[6] Thus, Passerini and Ugi reactions of glycosyl isonitriles would open up easy access to similar glycopeptide-like libraries.



Scheme 1. Products of Passerini and Ugi reactions of glycosyl isonitriles

As isonitrile compounds for Passerini and Ugi reactions we chose 2,3,4,6-tetra-*O*-acetyl- **1a** and 2,3,4,6-tetra-*O*-benzyl-*β*-D-glucopyranosyl isonitrile **1b**. Compound **1a** was obtained from 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl azide[7] *via* subsequent hydrogenolysis, formylation and dehydration as previously described.[2] Compound **1b** was prepared from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose[8] which was first converted into the corresponding *β*-D-glucopyranosyl amine[9] followed by formylation and dehydration with

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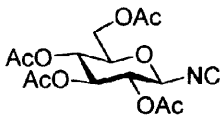
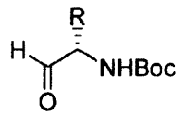
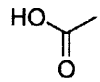
diphosgene according to previously described procedures.[10] Passerini reactions of isonitriles **1** were performed with *N*-Boc-glycinal **2a**, (*S*)-*N*-Boc-phenyl alaninal **2b** and propanal **2c** as the aldehyde compound and acetic acid **3a** as the acid compound. Ugi reactions with isonitriles **1** were perfomed with *i*-butanal **2d** as the aldehyde compound and with *N*-Boc-glycine **3b** and *n*-propyl amine **4a** in case of Ugi 4 center 4 compound reactions (U-4CR) and with (*S*)-serine in methanol, respectively in case of Ugi 5 center 4 compound reactions (U-5C-4CR). The results of these reactions are summarized in table 1.



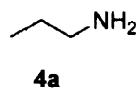
1a



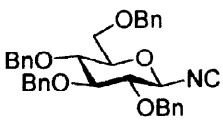
2a R = H
2b R = CH_2Ph



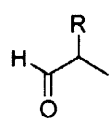
3a



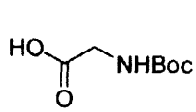
4a



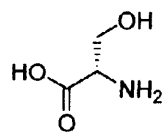
1b



2c R = H
2d R = CH_3



3b



4b

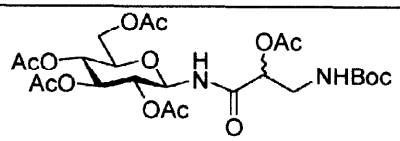
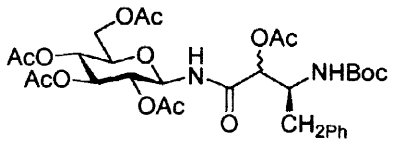
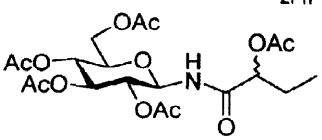
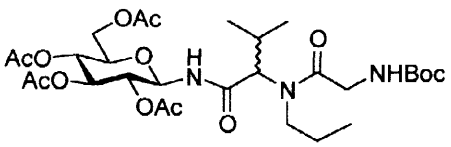
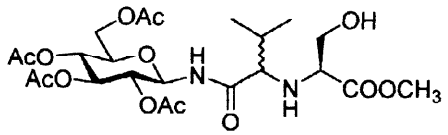
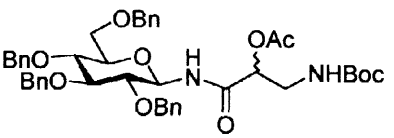
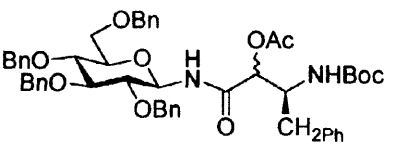
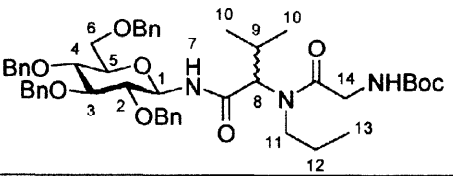
In general, Passerini reactions of anomeric glycosyl isonitriles **1** with glycinal and phenyl alaninal derivatives **2a** and **2b**, respectively (Table 1, entries 1,2,6 and 7) proceeded slowly and afforded the corresponding products only in medium yield. Obviously, Passerini reactions of glycosyl isonitriles are sensitive to steric effects of the aldehyde compound. This was evident from the reaction of **1a** with propanal **2c** which gave the Passerini product in good yield and resonable reaction time. All Passerini reactions gave the corresponding products with virtually no diastereoselectivity. Even in the case of enantiomerically pure (*S*)-phenyl alaninal **2b**, no diastereoselectivity of the newly formed asymmetric center was observed (entries 2,7). Furthermore, electronic effects in the isonitrile compound did not have any significance for the Passerini reaction since acetyl protected glucosyl isonitrile **1a** was only slightly more reactive than the corresponding benzyl protected isonitrile **1b**.

Similarly to the Passerini reaction, the Ugi reactions of glycosyl isonitriles (entries 4,5 and 8) proceeded with low diastereoselectivity. It is well known from other Ugi reactions that neither the nitrile compound nor the acid compound have pronounced effects on the diastereomeric course of the reaction.[5a,11] In contrast, optically active aldehyde and amine components may be used for substrate-contolled Ugi reactions.[5] Thus, none of the U-4CR additions performed here (entries 4 and 8) showed significant diastereoselectivities. Solely in case of the U-5C-4CR variant (entry 5) where (*S*)-serine **4b** was used as amine component the reaction proceeded with a low selectivity. Further optimizations of these Ugi reactions by Lewis acid catalysis with respect to yield and diastereoselectivity are now under investigation. Nevertheless, the Ugi reaction of anomeric glycosyl isonitriles as presented here, gives easy access to complex *N*-glycopeptides.

In a typical example (Table 1, entry 8), a solution of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl isonitrile **1b** (312 mg, 0.57 mmol) in CH_2Cl_2 (5 ml) is added dropwise at 0°C to a solution of *i*-butanal **2d** (52 µl, 0.57 mmol), n-propylamine **4a** (47 µl, 0.57 mmol) and *N*-Boc-glycine **3b** (100 mg, 0.57 mmol) in CH_2Cl_2 (5 ml). The mixture is warmed to RT and stirred for 25 d. Concentration of the solution and chromatography

of the residue with 3:1 toluene/acetone afforded *N*-(*N'*-Boc-glycyl-*N''*-n-propyl-valinyl)-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosylamine (148 mg, 31%), the diastereomers of which are separated by chromatography with 20:1 CH_2Cl_2/acetone.[12,13]

Table 1. Passerini (entries 1-3,6 and 7) and Ugi reactions (entries 4,5 and 8) of glucosyl isonitriles **1**.

entry	R-NC	R-CHO	R-CO_2H	R-NH_2	solvent conditions	yield d.r.	product[12]
1	**1a**	**2a**	**3a**	-	CH_2Cl_2 3d RT	23% 55:45	
2	**1a**	**2b**	**3a**	-	CH_2Cl_2 3d RT	41% 58:42	
3	**1a**	**2c**	**3a**	-	CH_2Cl_2 24h RT	80% 50:50	
4	**1a**	**2d**	**3b**	**4a**	CH_2Cl_2 37d RT	22% 55:45	
5	**1a**	**2d**	**4b**	**4b**	MeOH 11h 55°C	15% 63:37[a]	
6	**1b**	**2a**	**3a**	-	CH_2Cl_2 6d RT	31% 57:43	
7	**1b**	**2b**	**3a**	-	CH_2Cl_2 8d RT	35% 52:48	
8	**1b**	**2d**	**3b**	**4a**	CH_2Cl_2 25d RT	35% 60:40[a]	

[a]Separation of diastereomers by chromatography is possible.

Acknowledgement

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12. All compounds gave satisfactory elemental analyses. D.r. values were determined by NMR spectroscopy and HPLC analysis of the diastereomeric products.
13. Typical spectroscopic data for product of entry 8 (for assignment see table 1): diastereomer I: $[\alpha]_D^{20}$ = +15.7 (*c* = 0.5, $CHCl_3$), ^1H NMR ($CDCl_3$) δ = 7.13-7.36 (m, 20 H, H^{Ph}), 5.32 (bs, 1 H, NHBoc), 5.12 (dd, 1 H, $J_{1,2}$ = 9.0 Hz, $J_{1,NH}$ = 9.2 Hz, H-1), 4.44-4.89 (m, 8 H, CH_2Ph), 3.79-3.92 (m, 2 H, H-14), 3.62-3.76 (m, 4 H, H-3,5,6), 3.46-3.55 (m, 1 H, H-4), 3.34-3.41 (m, 1 H, H-2), 2.90-3.16 (m, 2 H, H-11), 2.50-2.72 (brs, 1 H, H-9), 1.72-1.89 (brs, 1 H, H-8), 1.40-1.60 (m, 2 H, H-12), 1.45 (s, 9 H, Boc), 0.73-0.98 (m, 9 H, H-10, 13); diastereomer II: $[\alpha]_D^{20}$ = -22.3 (*c* = 0.9, $CHCl_3$), ^1H NMR ($CDCl_3$) δ = 7.12-7.34 (m, 20 H, H^{Ph}), 5.36 (bs, 1 H, NHBoc), 5.09 (dd, 1 H, $J_{1,2}$ = 9.0 Hz, $J_{1,NH}$ = 9.3 Hz, H-1), 4.44-4.86 (m, 8 H, CH_2Ph), 3.89-3.97 (m, 2 H, H-14), 3.67-3.76 (m, 4 H, H-3,5,6), 3.51-3.55 (m, 1 H, H-4), 3.36-3.43 (m, 1 H, H-2), 3.02-3.11 (m, 2 H, H-11), 2.41-2.56 (brs, 1 H, H-9), 1.72-1.94 (brs, 1 H, H-8), 1.37-1.61 (m, 2 H, H-12), 1.45 (s, 9 H, Boc), 0.77-0.98 (2 d, 6 H, H-10), 0.73 (t, 3 H, J = 7.3 Hz, H-13).