## STEREOSELECTIVE THERMAL GLYCOSYLATION OF 2-DEOXY-2-ACETOAMINO-3,4,6-TRI-O-ACETYL-α-D-GLUCOPYRANOSYL CHLORIDE

Mugio NISHIZAWA,\* Waka SHIMOMOTO, Fumiko MOMII, and Hidetoshi YAMADA

Faculty of Pharmacentucal Sciences, Takushama Bauri University, Yamashiro-Cho, Lokushami 770, Japan

**Abstract:** Thermal glycosylation of alcohols with 2-deoxy-2-acetoamino 3.4.6-tri-O-acetyl-glucopyranosyl chloride at relatively lower temperature gives rise to  $\beta$ -glycosides selectively, whereas higher temperature favor to give  $\alpha$ -glycosides

2-Acetoamino-2-deoxy- $\alpha$ - or  $\beta$ -D-glucopyranosides play an important role in organic and bioorganic chemistry. Among a variety of reported glycosylation procedures, traditional Koenigs-Knorr type reaction of 1-haloglucosamine derivatives and an acid catalyzed reaction of oxazoline derivatives have been the major process for the synthesis of glucosamine glycosides.<sup>14</sup> Recently we have developed a very simple thermal glycosylation procedure by using easily accessible glycosyl donor, glycosyl chlorides.<sup>57</sup> Glycosides are obtained in high yield by heating a neat mixture of glycosyl chloride and alcohol in the presence of acid scavenger, without using any metal salts. When this thermal process was applied for an amino-sugar chloride **1**, we found a dramatic stercoselectivity depending upon the reaction temperature. Relatively lower temperature is in favor for  $\beta$ -selective coupling, whereas  $\alpha$ -selective reaction occurred at higher reaction temperatures



Thermal glycosylations of 2-deoxy-2-acetoamino-3,4,6-tri-*O*-acetyl-o-D-glucopyranosyl chloride (**1**) with cholesterol (**2**) or methyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (**3**) have been investigated in the presence of α-methylstyrene (α-MS) or *N N N'*.*N'*-tetramethylurea (TMU) as acid scavengers at a variety of reaction temperatures. For example, a dried neat mixture of **2** and **1** (3 equiv) in the presence of α-MS (3 equiv) was heated at 60°C until the alcohol was consumed (21 h), giving rise to β-glycoside,  $|\alpha|_0^{-5}$  -22° (*c* 0.75. CHC1.), & 4.86 (d, J = 8.2 Hz), in high yield and high selectivity ( $\alpha\beta$ 5.95) (run 1). TMU was equally acceptable as acid scavenger to give β-glycoside at 60°C, but longer reaction period was required for completion of the glycosylation (run 7). α-Glycoside,  $|\alpha|_0^{-5}$  +78° (*c* 0.14, CHCl<sub>3</sub>), & 4.97 (d, J = 3.8 Hz), was obtained predominantly at 160°C for shorter reaction period (run 6 and 9), along with cholesteryl acetate. Glycosylations of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**3**) at 60, 120 and 160°C in the presence of α-MS or TMU were also examined  $\beta$ -Selective coupling  $|\alpha|_0^{-23} + 3^{\circ}$  (*c* 0.9, CHCl<sub>3</sub>), & 4.30 (d, J = 7.7 Hz), 4.76 (d, J = 8.3 Hz), was observed at  $60^{\circ}$ C (run 10, 13), and α-glycoside,  $|\alpha|_0^{-21} + 40^{\circ}$  (*c* 0.19, CHCl<sub>3</sub>), & 4.33 (d, J = 8.3 Hz), 4.82 (d, J = 3.3 Hz), was selectively obtained at 160°C (run 12, 15).

Although the substrate  $\mathbf{3}$  contains a  $\beta$ -O-glycosidic linkage, isometrzation of the anometric configuration

was not observed during the thermal glycosylation. Upon heating of the isolated  $\beta$ -glycosidic product to 160°C, isomerization was not detected also. Thus the reaction is controlled kinetically with neighboring group participation at 60°C to give  $\beta$ -glycoside, whereas an  $\alpha$ -products were resulted at 160°C via free oxonium cationic intermediate without participation of the acetyl group. Occurrence of acetates at higher temperature are still mysterious

					yield (%)		
run	acceptor	acid scavenger	temperature	time (h)	acetate	glucoside	$\alpha/\beta$ ratio
1	2	α-MS	60	21	1	95	5.95
2	2	α-MS	80	10	2	98	28 72
3	2	α-MS	100	1	3	94	30.70
4	2	α-MS	120	0.75	19	79	64:36
5	2	α-MS	140	1	18	76	85.15
6	2	α-MS	160	0.3	13	64	88.12
7	2	TMU	60	72	18	82	6,94
8	2	TMU	120	2	28	64	29:71
9	2	TMU	180	0.25	39	46	83:17
10	3	α-MS	60	10	1	95	3:97
11	3	α-MS	120	1	6	64	10.90
12	3	α MS	160	0.17	25	32	96.4
13	3	TMU	60	10	2	86	7.93
14	3	TMU	120	2	19	45	38:62
15	3	TMU	160	1	20	37	83.17

Table I. Thermal glycosylation of 2-deoxy-2-acetoamino-3,4,6-tri-O-acetyl- $\alpha$ -D glucopyranosyl chloride (1).

4,4-Dimethyl-3 hydroxydecaline system is a popular skeletal system in natural products, and is recognized one of the severely hindered alcohols toward glycosylation. We have previously reported the structural and synthetic studies of seco-onoceranoid triterpenes and their glycosides isolated from *Lansium domesticum*<sup>8/11</sup> Therefore the  $\beta$ -selective thermal glycosylation was applied for the synthesis of Lansioside A (5). Thermal coupling of methyl lansiolate (4) and 1 (5 equiv) in the presence of TMU (5 equiv) at 60°C for 36 h afforded a  $\beta$ -glycoside in 40% yield along with 3% of an  $\alpha$  isomer. The former was identified with natural product derived lansioside A methyl ester triacetate (6). When the thermal reaction of 4 and 1 was carried out in the presence of  $\alpha$ -MS, double bond migration occurred to give a complicated mixture. This result suggests that TMU is suitable for acid sensitive substrates and the other case  $\alpha$ -MS is convenient.



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