Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 611–613
Tetrahedron Letters

An unprecedented *N*-transacylation reaction on 2-acetamido-2-deoxy-α-D-glucopyranosides

Yingxia Li,[a,*] Chunxia Li,[a] Peng Wang,[a] Shidong Chu,[a] Huashi Guan[a] and Biao Yu[b,*]

[a]*Institute of Food and Marine Drugs, Ocean University of China, Qingdao 266003, China*
[b]*State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

Received 14 August 2003; revised 17 October 2003; accepted 22 October 2003

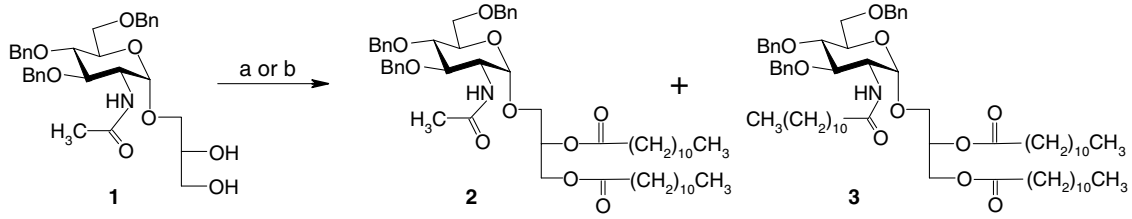
Abstract—An unprecedented *N*-transacylation reaction on 2-acetamido-2-deoxy-α-D-glucopyranosides was disclosed in the presence of acyl chloride and DMAP under reflux in pyridine.

2-Acetamido-2-deoxy-D-glucose, which constitutes chitin, is one of the most abundant monosaccharides in nature. It also appears in many other important poly- and oligosaccharides, including peptidoglycans and mucopolysaccharides (hyaluronic acids, keratan sulfates, and inner and outer core regions of glycoproteins) of animals, lipopolysaccharides of bacteria, and nodulation factors of rhizobia.[1] Replacement of the *N*-acetate with long chain acyl groups occurs in the lipopolysaccharides[2] and nod factors,[3] where the fatty acid moieties are crucial to their biological functions. It is noted that a variety of the synthetic *N*- and *O*-acylated glucosamine derivatives demonstrate immuno-modulating effects of potentially clinical usefulness.[4] From a synthetic point of view, replacement of an *N*-acetate with another acyl group calls for cleavage of the *N*-acetate first followed by acylation of the resulting $-NH_2$. Cleavage of the *N*-acetate requires harsh conditions that are marginally applicable to sugar derivatives. *N*-Transacylation, in which one *N*-acyl substituent is directly converted into another, has been achieved in only a few cases. Phenyl acetamides were converted into trifluoroacetamides with CF_3COOH or $(CF_3CO)_2O$ at high temperature in the presence of acidic catalysts such as $AlCl_3$[5] and zeolides.[6] Similar acidic conditions ($CF_3COOH/(CF_3CO)_2O$, 100 °C, 48 h) were mentioned to convert methyl 2-*N*-Ac-α-D-glucopyranoside into the 2-*N*-trifluoroacetate derivative.[7] Barrett found that the *N*-phenylacetyl side chain of penicillin and cephalosporin esters was readily exchanged by a trifluoroacetyl group on reaction with $(CF_3CO)_2O$ and subsequently DBN (1,5-diazabicyclo-[4,3,0]-non-5-ene), where the *N*-phenylacetyl group was in fact cleaved via a β-elimination.[8] We report here a ready *N*-transacylation reaction on 2-acetamido-2-deoxy-α-D-glucopyranosides in the presence of acyl chloride and DMAP under reflux in pyridine.

In the course of preparing glycoglycerolipids,[9] we found that treatment of 3-*O*-(2-acetamido-2-deoxy-α-D-glucopyranosyl)-*sn*-glycerol (**1**) with acyl chlorides (3.0 equiv), representatively lauryl chloride, in the presence of a catalytic amount of DMAP (*N*,*N*-dimethyl-4-aminopyridine) in pyridine at reflux for 30 min provided the desired di-*O*-acylation product **2** in a nearly quantitative yield (99%) (Scheme 1). However, longer reaction time resulted in a side product, which was characterized to be surprisingly the *N*-transacylation product **3**. Employing 5.0 equiv of lauryl chloride at reflux for 5 h gave **3** as the major product in 63% yield (31% yield for **2**). Such an *N*-transacylation reaction is unprecedented. The previous reported *N*-transacylations lead exclusively into the *N*-trifluoroacetate derivatives involving either strong acidic conditions or elimination of the *N*-phenylacetyl group bearing an acidic β hydrogen.[5–8] We thus examined the scope of this interesting transformation. The preliminary results were shown in Table 1.

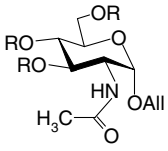
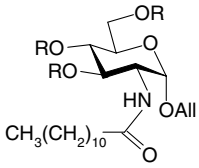
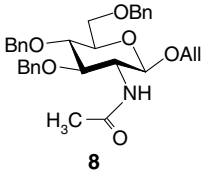
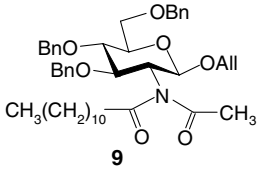
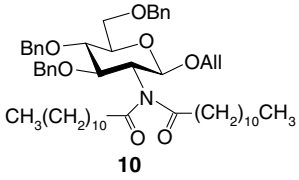
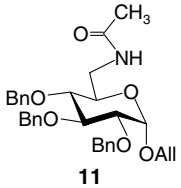
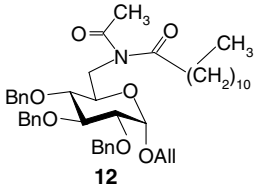
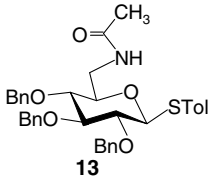
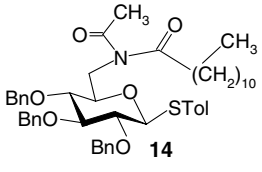
Keywords: *N*-Transacylation; 2-Acetamido-2-deoxy-α-D-glucopyranosides; Acyl chloride.
* Corresponding authors. E-mail: liyx417@mail.ouc.edu.cn; byu@mail.sioc.ac.cn

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.10.206



Scheme 1. (a) $CH_3(CH_2)_{10}COCl$ (3.0 equiv), DMAP (0.07 equiv), pyridine, reflux, 30 min, **2** (99%). (b) $CH_3(CH_2)_{10}COCl$ (5.0 equiv), DMAP (0.1 equiv), pyridine, reflux, 5 h, **2** (31%), **3** (63%).

Table 1. *N*-Acylation reactions of acetamido-sugars

Entry	Acetamido-sugars	Conditions[a]	Products (yields)[b]	
1	 **4** R = Bn **6** R = Ac	$C_{11}H_{23}COCl$ (1.0 equiv)	 **5** R = Bn **7** R = Ac	**5** (46%); **4** (46%)
2		$C_{11}H_{23}COCl$ (3.0 equiv)		**5** (67%); **4** (26%)
3		$C_{11}H_{23}COCl$ (9.0 equiv)		**5** (88%); **4** (trace)
4		$C_{11}H_{23}COCl$ (1.0 equiv)		**7** (30%); **6** (44%)
5		$C_{11}H_{23}COCl$ (3.0 equiv)		**7** (51%); **6** (23%)
6	 **8**	$C_{11}H_{23}COCl$ (1.0 equiv)	 **9**	**9** (33%); **8** (64%)
7		$C_{11}H_{23}COCl$ (2.0 equiv)	 **10**	**9** (68%); **10** (20%)
8	 **11**	$C_{11}H_{23}COCl$ (2.0 equiv)	 **12**	**12** (83%); **11** (trace)
9	 **13**	$C_{11}H_{23}COCl$ (2.0 equiv)	 **14**	**14** (66%); **13** (31%)
10		$C_{11}H_{23}COCl$ (6.0 equiv)		**14** (82%); **13** (trace)

[a] Conditions: lauryl chloride, DMAP (0.1 equiv), pyridine, reflux, 2 h.
[b] Isolated yields.

The reaction of allyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (**4**) with lauryl chloride (1.0 equiv) in the presence of DMAP (0.1 equiv) in pyridine at reflux was monitored by TLC. The *N*-trans-

acylation product **5** was the only product, which was produced gradually and reached a maximum yield at 2 h. Careful isolation gave **5** in 46% yield together with the recovered **4** (46%). The corresponding *N*,*N*-diacyl product, which might be the intermediate[5–8] was not detected (entry 1). Increasing the amount of lauryl chloride (3.0 and 9.0 equiv) in the reaction increased the final yield of **5** parallely (67% and 88%, respectively, entries 2 and 3), implying a reversible reaction involved. The 3,4,6-tri-*O*-acetyl counterpart **6** underwent similar *N*-transacylation to produce **7** as the major product (entries 4 and 5). However, treatment of the β-counterpart **8** under similar conditions did not lead to the *N*-transacylation product; instead, the products identified were the *N*-acetyl-*N*-lauryl derivative **9** and *N*,*N*-dilauryl derivative **10** (entries 6 and 7). These results implied that the congested 2-*N*,*N*-di-acyl derivatives of the α-D-glucopyranoside were sensitive toward the present conditions, therefore decomposed quickly into the 2-*N*-mono-acyl products (entries 1–5); while the 2-*N*,*N*-di-acyl derivatives (**9**, **10**) of the β-D-glucopyranoside were relatively stable. Then we examined the reactions with **11** and **13**, which bear the acetamido function at C-6. The 6-*N*-acetyl-*N*-lauryl derivatives **12** and **14** were produced as the predominant products, with no *N*-transacylation product being detected, nor the acyl exchanging *N*,*N*-di-lauryl derivative (cf. **10**) (entries 8–10). These results could be explained by the fact that the 2-*N*,*N*-di-acyl function, which is adjacent to the electron withdrawing acetal, is labile toward the present conditions. Thus cleavage of one of the 2-*N*-acyl substituent proceeds, while the remote 6-*N*,*N*-di-acyl function remains stable.

In summary, an unprecedented *N*-transacylation reaction was disclosed in the presence of acyl chloride and DMAP under reflux in pyridine, which took place specifically on the 2-acetamido-2-deoxy-α-D-glucopyranosides. Extension of the present reaction to other substrates such as oligosaccharide derivatives is our current interest.

Acknowledgement

We thank the financial support from the National Basic Research Program of China (2003CB716400).

References and Notes

1. Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev.* **1992**, *92*, 1167–1195.
2. Kusumoto, S.; Fukase, K.; Oikawa, M.; Suda, Y. *J. Chin. Chem. Soc.* **2002**, *49*, 453–458.
3. D'Haeze, W.; Holsters, M. *Glycobiology* **2002**, *12*, 79R–105R.
4. (a) Johnson, D. A.; Baldridge, J. R.; Sowell, C. G.; Cluff, C. W. US Patent: 65,25,028 B1, 2003; CA 138:153772; (b) Anastassiades, T. P. WO Patent: 2,002,017,890 A2, 2002; CA 136:210563; (c) West, M.; Meutermans, W.; Adamson, G.; Schafer, K.; Schliebs, D. WO Patent: 2,002,032,915 A1, 2002; CA 136:325779.
5. (a) Michman, M. J.; Patai, S.; Shenfeld, I. *J. Chem. Soc., C* **1967**, 1337–1340; (b) Michman, M.; Meidar, D. *J. Chem. Soc., Perkin Trans. 2* **1972**, 300–304; (c) Sonawane, H. R.; Pol, A. V.; Nanjundiah, B. S.; Sudalai, A. *J. Chem. Res. Synop.* **1998**, 90–91.
6. Sonawane, H. R.; Pol, A. V.; Moghe, P. P.; Sudalai, A.; Biswas, S. S. *Tetrahedron Lett.* **1994**, *35*, 8877–8880.
7. Nilsson, B.; Svensson, S. *Carbohydr. Res.* **1978**, *62*, 377–380.
8. Barrett, A. G. M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1629–1633.
9. Li, C. X.; Li, Y. X.; Yu, L. B.; Zhang, H.; Chu, S. D.; Guan, H. S. *Chin. Chem. Lett.* **2003**, *14*, 776–778.