New Synthetic Methods and Reagents for Complex Carbohydrates. II. Synthesis of 2-Acylamino-2-deoxy-D-glucopyranose Derivatives by Dimethylphosphinothioic Mixed Anhydride Method

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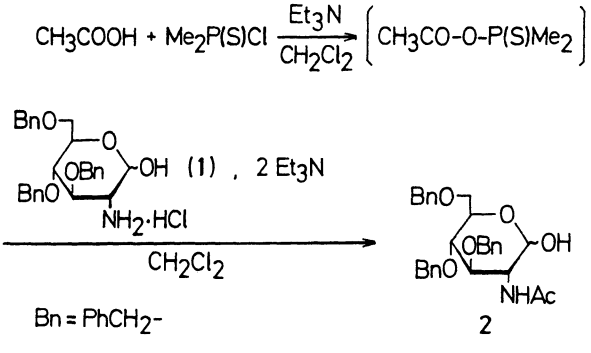
Synopsis. Dimethylphosphinothioic (Mpt) mixed anhydrides of carboxylic acids were found to be useful for *N*-acylation of 2-amino-2-deoxy-D-glucopyranose derivatives without protecting the hydroxyl functions. By this method, *N*-acylation of 2-amino-2-deoxy-D-glucopyranose hydrochloride in methanol was also found to be possible.

In recent years, *N*-acyl derivatives of amino sugars became interesting substances in biochemical studies. In order to study their structure-activity relationship etc., analogs of amino sugars which have various acyl group are desired. Symmetrical anhydrides are widely used for the *N*-acylation of amino sugars.[1,2] However, it seems difficult to introduce various acyl groups into the amino group without protecting the hydroxyl functions in sugars and acyl groups. For example, it was reported that 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (**2**) was prepared by the deprotection of *O*-acetyl group from *N,O*-diacetate which was derived from 2-amino-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (**1**) and acetic anhydride.[2]

Recently, it has been reported that the dimethylphosphinothioic (Mpt) mixed anhydride method is useful for the synthesis of peptides containing hydroxyamino acids without protecting the hydroxyl functions.[3] In this paper, we wish to describe an efficient and general *N*-acylation of 2-amino-2-deoxy-D-glucopyranose derivatives by Mpt mixed anhydrides which were derived from the corresponding carboxylic acids and dimethylphosphinothioyl chloride (Mpt-Cl).[4]

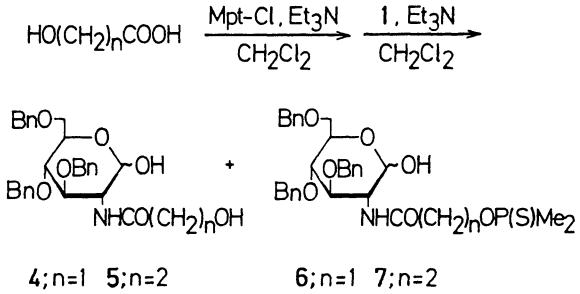
Results and Discussion

First, the reactivity of the Mpt mixed anhydride with hemiacetal hydroxyl group, which had not been previously reported, was investigated by the *N*-acylation of **1**. Mpt acetic anhydride was synthesized from Mpt-Cl and acetic acid in the presence of triethylamine in dichloromethane. It could be detected by silica-gel thin-layer chromatography (TLC). To this reaction mixture, compound **1** and 2 equiv of triethylamine were added and the resulting solution was stirred overnight at room temperature. The usual work-up gave the desired *N*-acetyl derivative (**2**) in quantitative yield. Similarly, the *N*-benzoyl derivative (**3**) was obtained in 86% yield. During these reactions no 1-*O*-acyl derivative could be detected by TLC.

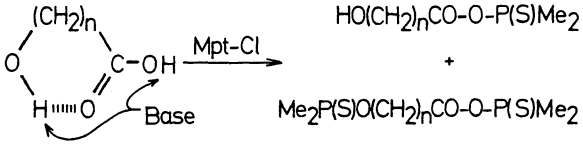


Next, we studied *N*-hydroxyacylation of **1** using Mpt mixed anhydrides according to a procedure similar to those described above. *N*-Hydroxyacyl amino sugars are found in complex carbohydrates, such as lipid A, *N*-glycoloyl neuraminic acid. Usually for the *N*-hydroxyacylation, *O*-protected acylation reagents were used.[5,6] However, by the Mpt mixed anhydride method *N*-hydroxyacylation without protecting the hydroxyl function in the acyl group was anticipated to occur.

In spite of the poor reactivity of Mpt-Cl with alcohol,[3] the mixture of the desired *N*-hydroxyacyl derivatives (**4**, **5**) and the corresponding *O*-dimethylphosphinothioyl derivatives (**6**, **7**) were obtained unexpectedly in the case of glycolic acid and 3-hydroxypropanoic acid in accord with following equation.



This side reaction suggested that Mpt-Cl might react with the hydroxyl group in carboxylic acid, which was activated by the formation of intramolecular hydrogen bond, to give two mixed anhydrides. In fact, these two mixed anhydrides could be detected by TLC. Therefore, we expected that this side reaction could be overcome if a polar solvent and a low nucleophilic base were used.



Based on this hypothesis, we studied the *N*-glycoloylation of **1**, and found *N,N*-diisopropylethylamine (DIEA) in tetrahydrofuran (THF) effective to promote selective *N*-acylation. On the other hand, we also found that the *N*-glycoloyl derivatives (**4**) could not be obtained in good yield by the reaction of gly-

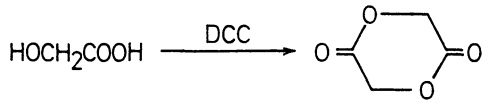
Table 1. *N*-Glycoloylation of **1** by Mpt Mixed Anhydride

Base	Solvent	Yield/%	
		3	**5**
Et_3N	CH_2Cl_2	Mixture	
Et_3N	THF	87	Trace
DIEA	CH_2Cl_2	84	Trace
DIEA	THF	84	0

Table 2. *N*-Acylation of **1** by Mpt Mixed Anhydride

Acyl group	Yield/%
Ac-	quant.
Bz-	86
$HOCH_2CO$-	84
$HO(CH_2)_2CO$-	68
$HO(CH_2)_{15}CO$-	78

colic acid and **1** using dicyclohexylcarbodiimide (DCC). To clarify this point, we attempted the synthesis of the symmetrical anhydride of glycolic acid by DCC according to the literature[5] and found that 1,4-dioxane-2,5-dione (**8**) was obtained as the main product.



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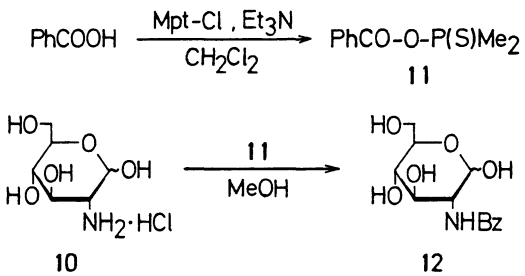
In a similar manner using Mpt mixed anhydrides, *N*-(3-hydroxypropanoyl) and *N*-(16-hydroxyhexadecanoyl) derivatives (**5**, **9**) were obtained in good yields. The results described above are summarized in Tables 1 and 2.

Finally, we applied this method to the *N*-benzoylation of 2-amino-2-deoxy-D-glucopyranose hydrochloride (**10**) in methanol. In order to simplify the reaction system the benzoyl Mpt mixed anhydride was purified by means of silica-gel flash-column chromatography to give colorless crystals **11** in 93% yield. The reaction of compound **10** and Mpt mixed anhydride **11** in the presence of various bases in methanol was tried. The desired 2-benzamido-2-deoxy-D-glucopyranose (**12**) was obtained in 76% yield as colorless crystals by using of DIEA. On the contrary, in the case of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), only benzoic acid was obtained. These results suggested that the nucleophilicity of the base might be an important factor for this reaction.



10 **12**

According to the present method, various *N*-acyl derivatives of 2-amino-2-deoxy-D-glucopyranose could be synthesized in good yields. It should be noted that the protection of the hydroxyl functions in acyl groups and sugars was not necessary and further, this *N*-acylation could be carried out in an alcoholic solvent, such as methanol.

Experimental

Mp's were uncorrected. Optical rotations were measured at 26—29 °C after being kept overnight at room temperature.

Typical Procedure for *N*-Acylation of 1. To a mixture of carboxylic acid (0.2 mmol) and 0.2 mmol of base (triethylamine or DIEA) in dichloromethane or THF (1 mL) was added a solution of Mpt-Cl (25.7 mg; 0.2 mmol) in the solvent (1 mL) under ice-cooling. After stirring for 30 min, the formation of Mpt mixed anhydride could be confirmed by TLC, then compound **1** (97.2 mg; 0.2 mmol) and the base (0.4 mmol) were added to it. The resulting mixture was stirred overnight at room temperature. Usual work-up followed by evaporation and preparative thin-layer chromatography gave the desired *N*-acyl derivatives in good yield.

2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (2). 98.3 mg (100%): Mp 216—217 °C (lit; 216—219 °C);[7] $[\alpha]_D$ +67.2° (*c* 1.08, $CHCl_3$) (lit; +71.3° (*c* 1.08, $CHCl_3$)).[2]

2-Benzamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (3). 95.2 mg (86%): Mp 215—217 °C (lit; 215—217 °C);[8] $[\alpha]_D$ +80.8° (*c* 0.48, pyridine) (lit; +88.6° (*c* 0.48, pyridine)).[8]

3,4,6-Tri-*O*-benzyl-2-deoxy-2-glycoloylamino-D-glucopyranose (4). 84.8 mg (84%): Mp 204—206 °C; $[\alpha]_D$ 40.0° (*c* 0.4, 10% MeOH/$CHCl_3$). Found: C, 67.08; H, 6.46; N, 2.65%. Calcd for $C_{29}H_{33}NO_7 \cdot 1/2H_2O$: C, 67.43; H, 6.63; N, 2.71%.

3,4,6-Tri-*O*-benzyl-2-deoxy-2-(3-hydroxypropanoylamino)-D-glucopyranose (5). 70.0 mg (68%): Mp 191—194 °C; $[\alpha]_D$ +51.2 (*c* 1, $CHCl_3$). Found: C, 68.23; H, 6.70; N, 2.66%. Calcd for $C_{30}H_{35}NO_7 \cdot 1/2H_2O$: C, 67.91; H, 6.84; N, 2.64%.

3,4,6-Tri-*O*-benzyl-2-deoxy-2-(16-hydroxyhexadecanoylamino)-D-glucopyranose (9). 109.5 mg (78%): Amor.; $[\alpha]_D$ +20.0° (*c* 0.4, 20% $CHCl_3$/MeOH). Found: C, 72.14; H, 8.69; N, 2.08%. Calcd for $C_{43}H_{61}NO_7 \cdot 1/2H_2O$: C, 72.44; H, 8.77; N, 1.96%.

2-Benzamido-2-deoxy-D-glucopyranose (12). To the mixture of compound **10** (107.8 mg; 0.5 mmol) and DIEA (0.19 mL; 1.5 mmol) in methanol (4 mL) was added the solution of benzoic Mpt mixed anhydride (160.7 mg; 0.75 mmol) in 1 mL of methanol. After stirring overnight at room temperature, the methanol was evaporated in vacuo. The residue was dissoleved in water and adsorbed on Dia-ion HP-20. The resin was washed with water and eluted with methanol and evaporated. The residue was purified by preparative thin-layer chromatography using the chloroform-methanol-acetic acid (85 : 25 : 20) solvent system. The desired band was eluted with methanol and evaporated in vacuo. The residue was dissolved in methanol, placed in a Sephadex LH-20 column (2×100 cm), and eluted with methanol. The desired fractions were collected to yield **10** as colorless crystals (107.6 mg, 76%). Mp 198 °C (decomp) (lit; 198—200 °C);[9] $[\alpha]_D$ +29.2° (*c* 1, H_2O) (lit; +35.0° (*c* 2, H_2O)).[9] The similar procedure using 1 equiv of **11** in the presence of 2 equiv of Et_3N or DIEA gave **12** in 58, 62% yield, respectively. On the other hand, when 2 equiv of DBU was used only benzoic acid was recovered.

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