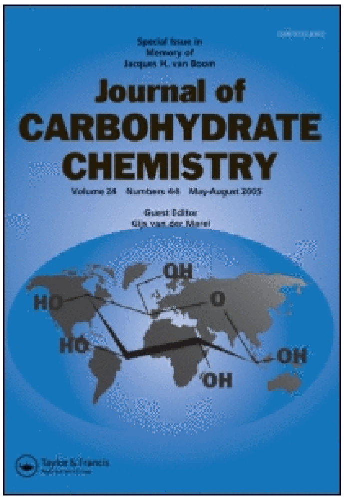

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Oscar Moradei[a]; Silvana Leit[a]; Cecile du Mortier[a]; Alicia Fernandez Cirelli[a]; Joachim Thiem[b]
[a] Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Buenos Aires, Argentina [b] Institut für Organische Chemie, Universität Hamburg, Germany

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AMINE-INDUCED DEACYLATION OF CARBOHYDRATE DERIVATIVES UNDER ANHYDROUS CONDITIONS[≠]

Oscar Moradei,[1] Silvana Leit,[1] Cecile du Mortier,[1] Alicia Fernández Cirelli[1*] and Joachim Thiem.[2]

[1]Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pab. II, Ciudad Universitaria, 1428, Buenos Aires, Argentina. [2]Institut für Organische Chemie, Universität Hamburg, Germany.

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ABSTRACT

Methanolysis of acylated carbohydrate derivatives was effectively performed using tertiary amines in the absence of water at room temperature. The reaction was performed with acetylated and benzoylated alditols, aldoses, lactones, orthoesters, glycosides, and disaccharides. *N*-methylpyrrolidine proved to be especially suitable for synthetic purposes and deacylated compounds were obtained in excellent yields. The mild conditions employed and the minimum work-up needed make this method appropriate for the deacylation of labile compounds.

INTRODUCTION

Transesterification reactions normally require acid or basic catalysis. Only in special cases may alcoholysis of an ester be performed under neutral conditions.[1] Since alcohol is employed as solvent, the reaction proceeds to completion in spite of its reversibility. It has been

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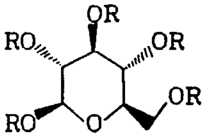
suggested that three types of catalysis (basic, nucleophilic and acidic) operate in transesterification reactions.[2]

Acyl groups are frequently used as protective groups in carbohydrate chemistry. Current deacylation methods employ strong acids or bases as catalysts.[3] Transesterification can also be achieved in milder conditions such as treatment with methanol-water-triethylamine (5:1:1) at room temperature,[4] but this method is inappropriate when anhydrous conditions are required for the subsequent steps in a synthetic pathway. If an inorganic base is used in an anhydrous solvent, i.e., potassium carbonate in anhydrous methanol,[5] desalting after the reaction may be disadvantageous when labile substituents are present.

RESULTS AND DISCUSSION

In the course of recent studies, deacylation of a carbohydrate orthoester was required under anhydrous conditions. Therefore, we investigated the methanolysis of different ester derivatives in the presence of tertiary amines in the absence of water at room temperature. Acetylated and benzoylated derivatives of alditols, aldoses, lactones, orthoesters, glycosides, and disaccharides were examined in this study.



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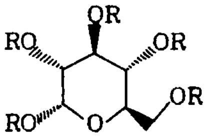
1b R=H



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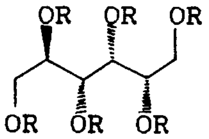
2b R=H



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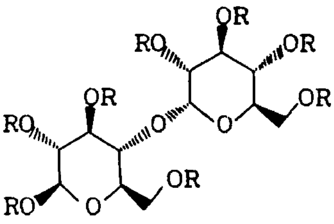

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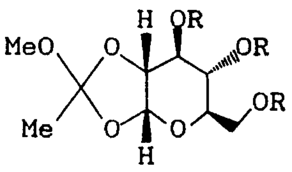

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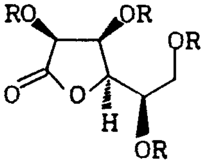

6a R=Ac
9a R=Bz
6b R=H

Experiments were performed with acetylated and benzoylated derivatives of carbohydrates in anhydrous methanol with different tertiary amines as catalysts. Triethylamine (TEA; pK_b 3.36), *N*-methylpyrrolidine (NMP; pK_b 3.83), tributylamine (TBA; pK_b 4.07) and 1,4-diazabicyclo[2.2.2]octane (DABCO; pK_b 5.40) were all found to be effective for the removal of acetyl groups in the absence of water at room temperature.

For benzoyl derivatives, different results were observed. For synthetic purposes, only NMP is useful since the other bases require long reaction times, at least seven days at room temperature. Shorter reaction times were observed at higher temperatures.

The basic catalytic effect of the tertiary amine promotes the formation of methoxide ion, which is more effective as nucleophile than methanol itself. The increased catalytic effect observed among NMP and TEA or TBA in debenzoylation cannot be explained by their differences in K_b. NMP is less hindered than TEA or TBA and can act as a nucleophilic catalyst. Nevertheless, the nucleophilic effect is only of secondary importance since, when DABCO was used as catalyst, longer reaction times were needed (at least 10 h for acetates) in spite of its higher nucleophilicity.

The carbohydrate derivatives assayed were: 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (**1a**), methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside (**2a**), hexa-*O*-acetyl-D-sorbitol (**3a**), 1,2,3,6-tetra-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-β-D-glucopyranose (octaacetylmaltose, **4a**), 3,4,6-tri-*O*-acetyl-1,2-methylorthoacetyl-α-D-glucopyranose (**5a**), 2,3,5,6-tetra-*O*-acetyl-D-mannono-1,4-lactone (**6a**), methyl 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside (**7a**) hexa-*O*-benzoyl-D-sorbitol (**8a**) and 2,3,5,6-tetra-*O*-benzoyl-D-mannono-1,4-lactone (**9a**).

In Table 1, experimental conditions and yields of methanolysis catalyzed by NMP are shown. Benzoylated

Table 1. Experimental Conditions Used for the Deacetylation of Compounds 1a-6a.[a]

Compound	Ratio NMP/CH_3OH [% v/v]	Time [h]	Product	Yield [%]
1a	0.16	8	**1b**	93
2a	0.12	11	**2b**	98
3a	0.24	12	**3b**	92
4a	4.90	19	**4b**	96
5a	0.88	14	**5b**	73
6a	5.10	15	**6b**	82

[a] At room temperature

Table 2. Physical constants for compounds 1b-6b.

Compound	$[\alpha_D]$ (c, solvent)	$[\alpha_D]$(lit.) (c, solvent)	mp ($^\circ$C)	mp (lit)	Ref
1b	$+52.6^\circ$ (1, H_2O)	$+52,7^\circ$ (3.9, H_2O)	146-155	145-146	7
2b	$+157.4^\circ$ (1, H_2O)	$+157^\circ$ (2, H_2O)	163-165	165-166	8
3b	-1.8° (1, H_2O)	-1.9° (10, H_2O)	87-92	95-96	9
4b	$+138.6^\circ$ (1, H_2O)	$+136^\circ$ (4,2, H_2O)	100-102	99-101	10
5b	$+52.0^\circ$ (1, CH_3OH)	-------	syrup	------	
6b	$+51.0^\circ$ (1, H_2O)	$+51.3^\circ$ (1, H_2O)	150-151	151	11

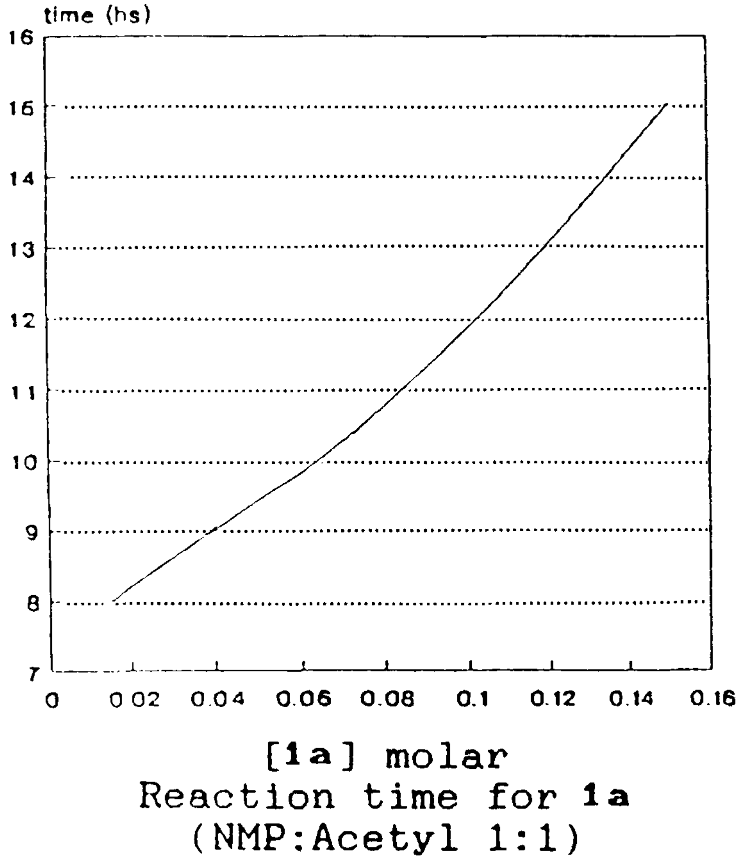

Fig. 1
Dependence of reaction time on substrate concentration of 1a

derivatives were dissolved in chloroform or THF prior to the addition of methanol to achieve homogeneous reaction media. If the reaction was conducted in methanol alone, longer reaction times were required. Deacylated compounds were characterized by their physical constants (Table 2). 1,2-Methylorthoacetyl-α-D-glucopyranose (5b) was further characterized by ^{13}C NMR spectroscopy.

Experiments in which penta-*O*-acetyl-β-D-glucopyranose was the substrate were conducted at different concentrations (FIG. 1). Shorter reaction times were observed in more

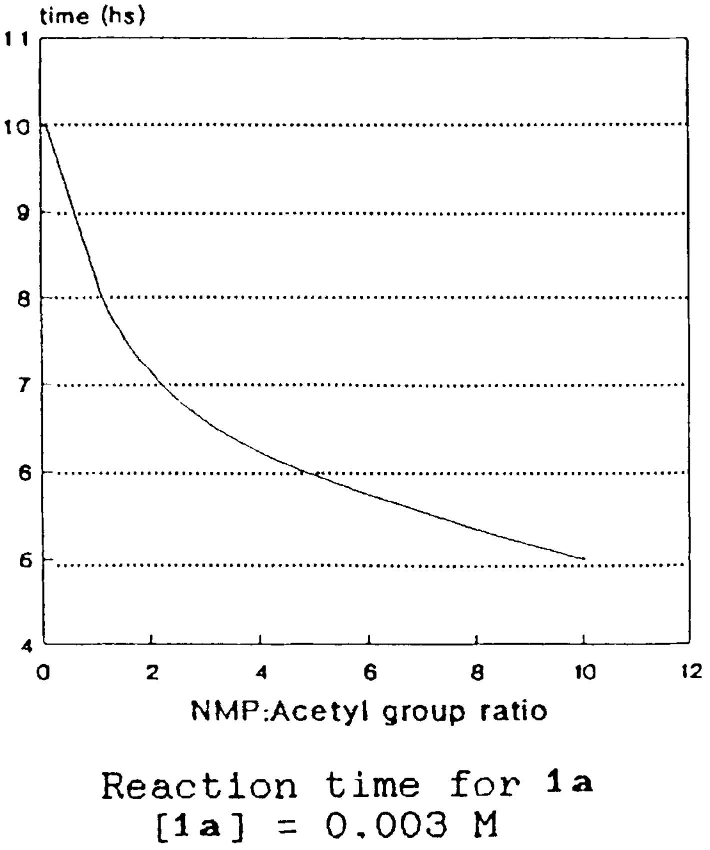

Fig. 2
Dependence of reaction time on
NMP/Acetyl group ratio

dilute solutions. An appropriate ratio of NMP to acetyl groups seems to be 2:1 since higher ammounts of base do not promote completion of the reaction in times significativelly shorter (FIG. 2).

In conclusion, the method described herein is synthetically attractive for the removal of acyl groups in carbohydrates. It compares favorably with known procedures since it can be employed for substrates bearing substituents labile to water or acid media. Best results were obtained with NMP in anhydrous methanol.

An additional advantage of this method is the easy recovery of the product from the reaction mixture by evaporation.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Optical rotations were recorded with a Perkin-Elmer 141 polarimeter. Column chromatography was performed on Silica Gel 60 (Merck). TLC was carried out on precoated aluminum plates (0.2 mm) of Silica Gel 60 F-254 (Merck). Detection was effected by exposure to UV light and by spraying the plates with 5% (v/v) H_2SO_4 in ethanol followed by heating. ^{13}C NMR spectra were recorded with a Varian XL-100 spectrometer at 25.2 MHz for solutions in acetone d-6.

Compounds **2a**-**9a** were prepared as described in the literature.[6]

General Procedures for the Deacetylation of

-1,2,3,4,6-Penta-*O*-acetyl-β-**D**-glucopyranose (**1a**)
-Methyl, 2,3,4,6-tetra-*O*-acetyl-α-**D**-glucopyranoside (**2a**)
-Hexa-*O*-acetyl-**D**-sorbitol (**3a**)
-1,2,3,6-Tetra-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-**D**-glucopyranosyl)-β-**D**-glucopyranose (octaacetylmaltose, **4a**)
-3,4,6-Tri-*O*-acetyl-1,2-methylorthoacetyl-α-**D**-glucopyranose (**5a**)
-2,3,5,6-tetra-*O*-acetyl-**D**-mannono-1,4-lactone (**6a**).

NMP was added to solutions of compounds **1a**, **2a**, **3a**, **4a**, **5a** and **6a** in dry methanol and the mixture was stirred under N_2 at room temperature, and monitored by TLC. The solvent was evaporated and the products were purified by column chromatography eluting with ethyl acetate-methanol (19:1).

The products obtained were: D-glucose (1b), methyl α-D-glucopyranoside (2b), D-sorbitol (3b), 4-*O*-α-D-glucopyranosyl-D-glucopyranose (4b), 1,2-methylorthoacetyl-α-D-glucopyranose (5b) and D-mannono-1,4-lactone (6b). Experimental conditions and yields of the products are shown in Table 1 and their physical constants are shown in Table 2.

^{13}C NMR data for compound 5b: 121.9 (C-1 ethylidene); 98.6 (C-1); 79.6 (C-2); 74.9 (C-3);74.7 (C-5); 70.2 (C-4); 63.0 (C-6); 49.8 (CH_3O); 23.3 (C-2 ethylidene, *exo)*

Debenzoylation of Methyl 2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranoside (7a). To a solution of methyl 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside (6a 0.145 g, 0.24 mmol) in anhydrous methanol (3.8 mL), tetrahydrofuran (0.95 mL) and NMP (0.21 mL) were added. The reaction was stirred at 60° C and monitored by TLC (hexane:ethyl acetate 5:2) After 36 h, dry toluene was added and the solution was concentrated. Recrystallization from isopropyl alcohol yielded methyl α-D-glucopyranoside (2b, 0.040 g, 87%).

Debenzoylation of Hexa-*O*-benzoyl-D-sorbitol (8b). To a solution of hexa-*O*-benzoyl-D-sorbitol (7, 0.25 g, 0.3 mmol) in THF (1.3 mL) and methanol (4.8 mL) under dry N_2 atmosphere, NMP (0.40 mL) was added. The reaction was carried out at 60 °C and was completed in 42 h as observed by TLC (ethyl acetate/methanol 5:2). The absence of partially benzoylated products was confirmed by paper chromatography in 1-butanol/pyridine/water (6:4:3) using an authentic sample of sorbitol. The solution was concentrated and after recrystallization from ethanol afforded pure sorbitol (3b 0.036 g, 65%).

Debenzoylation of 2,3,4,6-tetra-*O*-benzoyl-D-mannono-1,4-lactone (9a). To a solution of 2,3,5,6-tetra-*O*-benzoyl-D-mannono-1,4-lactone (9a, 27.5 mg, 0.5 mmol) in anhydrous methanol (0.7 mL), tetrahydrofuran (0.7 mL) and NMP (0.04 mL) were added. The reaction was stirred at 60 °C and monitored by TLC (ethyl acetate-ethanol-water 7:2:1). After

50h the solution was concentrated and the residue was purified by column chromatography eluting with ethyl acetate-methanol (19:1). Pure D-mannono-1,4-lactone (**6b**) was obtained in 59% yield.

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