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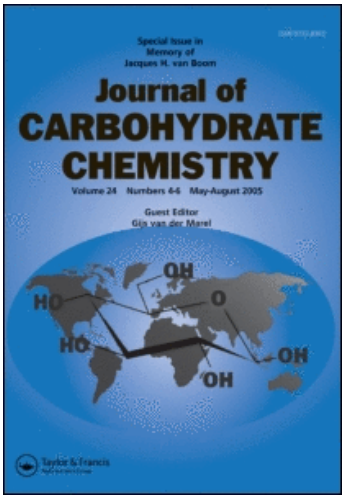

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Cecilia Elias[a]; María E. Gelpi[a]; Raúl A. Cadenas[a]
[a] Departamento de Quimica, Facultad de Agronomia Universidad de Buenos Aires, Buenos Aires, Argentina

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REACTION OF PERACYLATED SUGARS WITH NITRILES CATALYZED BY LEWIS ACIDS

Cecilia Elías, María E. Gelpi,
and Raúl A. Cadenas*

Departamento de Química, Facultad de Agronomía
Universidad de Buenos Aires, (1417) Av. San
Martín 4453, Buenos Aires, Argentina.

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ABSTRACT

The reaction of acetylaminoacetonitrile with penta-*O*-benzoyl-α-D-glucopyranose in dichloromethane-nitromethane, in a 1:1 stoichiometric proportion, catalysed by stannic chloride, gave a nitrilium salt that, after hydrolysis, afforded the corresponding *N*-acyl glycosylamine and a mixture of several compounds originating from different competitive reactions. Among these compounds, *N*-benzoyl-3,5,6-tri-*O*-benzoyl-β-D-glucofuranosyl amine, tetra-*O*-benzoyl-D-glucopyranose, and octa-*O*-benzoyl-β-D-glucopyranosyl-(1→1) -α-D-glucopyranoside (octa-*O*-benzoyl-α,β-trehalose) were identified.

INTRODUCTION

It is known that the reaction of nitriles with molecules possessing electropositive centres, might lead to very reactive nitrilium salts. Initially, the reaction of nitriles with polarized double bonds[1] or with halonium salts[2] was described; later, these studies were extended to polarized halogen-carbon bonds,[3] alkyl oxonium ions and dialkoxy carbocations,[4] as well as to alcohols activated by organic salts of antimony.[5]

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In the carbohydrate field the interaction between acetonitrile, when used as a solvent, and glycosyl oxocarbenium ions, formed from different glycosyl donors,[6,7,8,9] has been described. In some cases the acetonitrilium salts thus formed were intermediates in oligosaccharide synthesis,[7,8] or, alternatively, led to the formation of glycosylamido bonds,[6,9,10,11] oxazolines,[12] or rearranged to give a glucosylamine.[13]

RESULTS AND DISCUSSION

These previous results, centered on the use of acetonitrile, suggest the possibility that a peracylated sugar, activated in solution by stannic chloride, could react with other nitriles when added in stoichiometric proportion to give, after hydrolysis peracylated *N*-acylglycosylamines, as ilustrated in Scheme 1.

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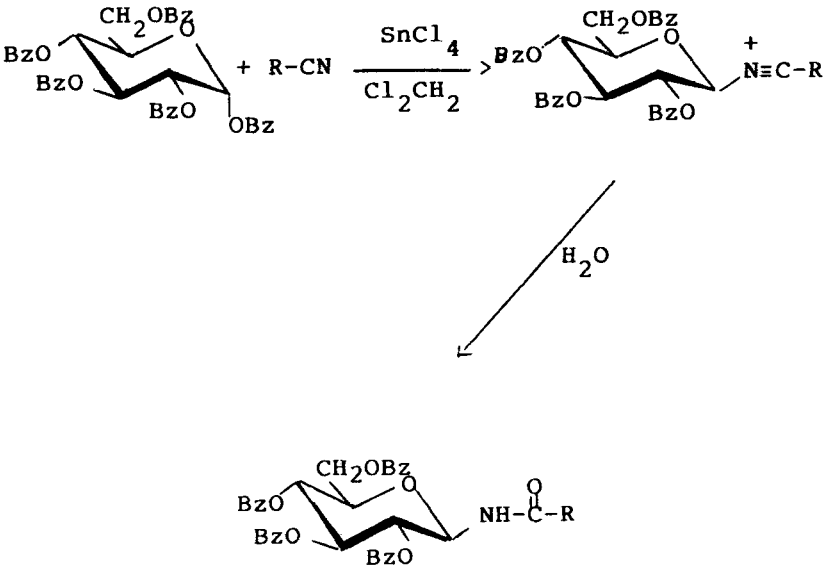
This type of reaction would allow direct synthesis of *N*-acylglycosylamines with structural versatility at the anomeric carbon atom, and of particular interest as to amino acid glycoconjugates *via* the corresponding nitriles. To evaluate this hypothesis we investigated the reaction of penta-*O*-benzoyl-α-D-glucopyranose with acetylamino acetonitrile in the presence of stannic chloride. The amino group in this reagent was in this case blocked by an acetyl group, but could in principle be blocked by any removable *N*-blocking group. To allow total solubility of the reactants, a mixture of dichloromethane-nitromethane was employed. After the reaction mixture was kept for 72 h at room temperature the solution was worked up to give a syrupy mixture of different compounds which were separated and purified by column and thin layer chromatography. The results showed that the desired coupling of reactants occurred to about 36% and the remaining products resulted from changes of the starting sugar, promoted by the catalyst.

Scheme 2 shows the different competitive pathways that could follow when penta-*O*-benzoyl-α-D-glucopyranose **(1)** was activated to give a reactive acyloxonium ion intermediate **2.** By coupling with acetylaminoacetonitrile the first formed adduct would react further with water through the resonance structures **4** and **5**. The reaction of **4** with water led after subsequent rearrangement to the expected *N*-(acetylaminoacetyl)-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosylamine **(7)** in 30% yield. The ^{1}H NMR spectrum of this substance showed $J_{1,2}$= 9.5 Hz indicating the β-anomeric configuration and the rest of the coupling constants confirmed a $^4C_1$ conformation for this compound.



Scheme 1

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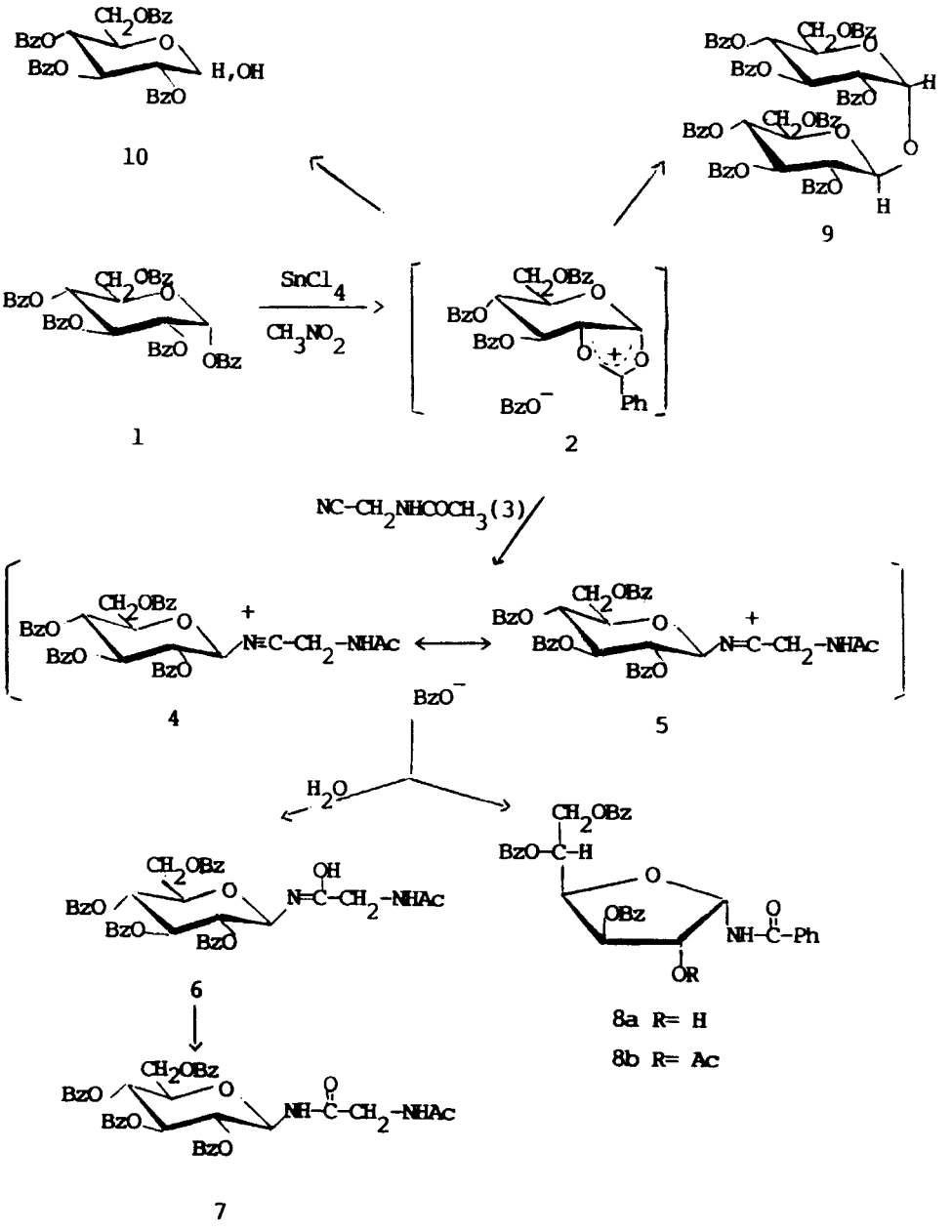
A second product, isolated in 6.2% yield, originating from the carbohydrate-nitrile intermediate, was the *N*-benzoyl-3,5,6-tri-*O*-benzoyl-α-D-glucofuranosylamine **(8)**. The structure of this unexpected compound was evident from its ^{1}H NMR spectrum and that of its 2-*O*-acetyl derivative, whose resonances were totally assigned by double irradiation. In **8a** the chemical shifts varied from what would be expected for a pyranose derivative, while they were in accord with shift values reported for hexofuranoses.[14] Thus, H-5 resonated at very low field (δ 5.76), suggesting that OH -5 was benzoylated. On the other hand, H-4 was shifted to a higher field (δ 4.38) than expected, if the pyranoid structure was maintained, indicating that OH-4 was involved in a furanoid ring. H-2 resonated at high field (δ 4.29) showing that OH-2 was not benzoylated, and it was the only proton that on acetylation shifted to lower field (δ 5.32). A broad singlet (δ 3.72) corresponding to the C-2 hydroxyl group dissappeared on acetylation. The H-1 H-2 coupling constant of 3.7 Hz indicated the α-anomeric configuration. Otherwise this value should be lower than 1 Hz.[15] The formation of this compound would imply a splitting of the nitrilium salt at the nitrile side chain level and benzoyl group migrations along the sugar backbone.



Scheme 2

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Other products isolated in the reaction resulted from autocondensations and rearrangements of the starting sugar. Thus, octa-*O*-benzoyl-β-D-glucopyranosyl-α-D-glucopyranoside (octa-*O*-benzoyl-α,β-trehalose, **9**, 5.3% yield), and 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranose (**10**, 8.5% yield) were obtained. These compounds would originate by reaction of the cyclic acyloxonium ion **2** with water, or by condensation of that ion with the 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranose produced in this same reaction. Formation of **9** could also occur *via* the nitrilium intermediate.

The octa-*O*-benzoyl-α,β-trehalose was obtained as an amorphous powder and the anomeric configuration was clearly defined by two doublets corresponding to H-1 at δ 5.67 ($J_{1,2}$ 3.6 Hz, α-configuration) and H-1' at δ 5.23 ($J_{1',2'}$ 7.7 Hz, β configuration). FAB^+ mass spectrometry showed the corresponding molecular ion at 1173 mass units.

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EXPERIMENTAL

General procedures. Melting points (Kofler hot-stage) are uncorrected. TLC was conducted on Silica Gel G (Merck) plates (0.25 mm layer thickness) with the following solvents: A) 19:1 (v/v) benzene-abs ethanol; B) 49:1 (v/v) benzene-abs ethanol; C) 17:3 (v/v) benzene-abs ethanol; D) 1:9 (v/v) ethyl acetate-benzene. The spots were detected with iodine vapor. Optical rotations were measured with a 141 Perkin-Elmer automatic polarimeter at 20 °C. IR spectra were recorded for Nujol mulls with a Perkin-Elmer 710 B spectrophotometer. ^1H NMR spectra were recorded with a Bruker ACE Spectrometer at 200 MHz with tetramethylsilane as the internal reference standard. Mass spectra were recorded in a VG spectrometer at 180 °C and 70 eV. FAB^+ mass spectrometry was conducted with a ZAB-SEQ spectrometer.

Acetylaminoacetonitrile. Aminoacetonitrile hydrochloride (1 g, 17 mmol) was dissolved in a mixture of pyridine (11 mL) and acetic anhydride (9.5 mL), the yellow solution was kept at room temperature for 48 h and then was concentrated to dryness to a syrup. TLC (solvent A) showed a principal spot at R_F 0.70. The syrup was purified by column chromatography on Silica Gel using acetone as eluant. The main fraction was a syrup which crystallized from toluene, mp 77-79 °C (1.054 g, 60% yield). ^1H NMR data (Py-d_5) δ 2.03 (s, 3H, CH_3CO), 4.48 (d, CH_2), 9.56 (NH).

Anal. Calcd for $C_4H_6N_2O$: C, 48.97; H, 6.12; N, 28.57. Found: C, 49.30; H, 6.40; N, 28.93.

Reaction of acetylaminoacetonitrile with penta-*O*-benzoyl-α-D-glucopyranose. Penta-*O*-benzoyl-α-D-glucopyranose (700 mg, 1.0 mmol) was dissolved in dichloromethane (3 mL) and stannic chloride (0.2 mL) was added. The solution was stirred at room temperature for 1 h and then acetylaminoacetonitrile (99 mg, 1.0 mmol) in dichloromethane (1 mL) was added. The solid that precipitated was dissolved by adding nitromethane (4 mL) and the solution was stirred for 72 h at room temperature. Then, the solution was diluted with nitromethane (70 mL) and shaken successively with an aqueous solution of sodium hydrogen carbonate (40 mL) and water (3 x 20 mL). The aqueous-nitromethane mixture was kept 24 h at room temperature, then the organic phase was decanted and dried with anhydrous sodium sulfate. The solution was concentrated to dryness to give a residue (519 mg) which was dissolved in benzene and chromatographed on a column of Silica Gel (Fluka 100) of 350 mm by 20 mm. Elution was conducted with benzene (700 mL, F_{1-3}) and increasing concentrations of ethanol in benzene as follows: 0.5% (1 L, F_4-F_{17}), 1% (1.5 L, F_{18}-F_{32}), 2.5% (600 mL, F_{33}-F_{38}), 5% (600 mL, F_{39}-F_{44}), 15% (600 mL, F_{45}-F_{47}), 30% (600 mL, F_{48}-F_{50}), ethanol (800 mL, F_{51}-F_{54}). The main products were obtained from F_{7-8} (212 mg) and F_{33-35} (207 mg). The rest of the fractions showed a distribution of products along the column, totalling 78 mg. The main products of the reaction were isolated and purified as follows.

***N*-(2-Acetylaminoacetyl)-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosylamine (7).** Compound 7 was obtained as an amorphous solid from fractions 33-35 by precipitation with ethanol: mp 196-199 °C (207 mg, 30% yield); $[\alpha]_D$ +45.00° (*c* 0.7, $CHCl_3$). TLC R_F 0.48 (solvent C). ^1H NMR ($DCCl_3$) δ 8.04-7.25 (20 H, benzoyl groups), 7.16 (anomeric NH, $J_{NH,1}$ 9.0 Hz), 6.01 (2 H, H-3, NH side chain, $J_{2,3}$= $J_{3,4}$ 9.5 Hz), 5.70 (t, H-4, $J_{3,4}$= $J_{4,5}$ 9.5 Hz), 5.66 (t, H-1, $J_{1,2}$= $J_{1,NH}$ 9.5 Hz), 5.38 (t, H-2), 4.60 (dd, H-6, $J_{5,6}$ 2.7 Hz, $J_{6,6'}$ 12 Hz), 4.45 (dd, H-6', $J_{5,6'}$ 4.4 Hz), 4.26 (m, H-5), 3.88 (d, CH_2), 1.99 (s, acetyl group).

Anal. Calcd for $C_{38}H_{34}N_2O_{11}$: C, 65.69; H, 4.93; N, 4.03. Found: C, 65.35; H, 5.03; N, 4.24.

***N*-Benzoyl-3,5,6-tri-*O*-benzoyl-α-D-glucofuranosylamine (8).** From fractions 21-24, compound **8** was obtained as a syrup that solidified as a powder by trituration with

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cold water: $[\alpha]_D$ +13.60° (*c* 0.5, $CHCl_3$); (37 mg, 6.2% yield). TLC R_F 0.31 (solvent A). ^1H NMR ($DCCl_3$) δ 8.03-7.38 (20 H, benzoyl groups), 6.71 (d, NH, $J_{1,NH}$ 9.2 Hz), 5.98 (dd, H-1, $J_{1,2}$ 4.2 Hz), 5.76 (m, H-5), 5.39 (dd, H-3, $J_{2,3}$ 1 Hz, $J_{3,4}$ 3.4 Hz), 4.85 (dd, H-6, $J_{5,6}$ 3.01 Hz, $J_{6,6'}$ 12 Hz), 4.38 (dd, H-4, $J_{3,4}$ 3.4 Hz, $J_{4,5}$ 7.3 Hz), 4.29 (dd, H-2 ,$J_{1,2}$ 4.2 Hz), 3.72 (broad s, OH).

Anal. Calcd for $C_{34}H_{29}NO_9.2H_2O$: C, 64.65; H, 5.26; N, 2.21. Found: C, 64.98; H, 5.56; N, 2.25.

Compound **8** was acetylated with a 1:1 mixture of pyridine-acetic anhydride (1.5 mL) at room temperature. The solution was concentrated to dryness and the residual syrup was dissolved in ethanol and the solution decolorized with charcoal. Evaporation of the solvent gave a syrup that turned to a powder by trituration with cold water. TLC gave a single spot R_F 0.38 (solvent A); $[\alpha]_D$ +11.0° (*c* 0.09, $CHCl_3$). ^1H NMR ($DCCl_3$) δ 8.06-7.33 (20 H, benzoyl groups), 6.22 (m, 2H, NH, H-1), 5.74 (m, H-5), 5.52 (dd, H-3, $J_{2,3}$ 1.0 Hz, $J_{3,4}$ 2.5 Hz), 5.32 (dd, H-2, $J_{1,2}$ 3.7 Hz), 4.85 (dd, H-6, $J_{5,6}$ 3.1 Hz, $J_{6,6'}$ 12.0 Hz), 4.51 (dd, H-6', $J_{5,6'}$ 6.4 Hz), 4.33 (dd, H-4, $J_{4,5}$ 7.9 Hz), 2.18 (s, acetyl group).

Anal. Calcd for $C_{36}H_{31}NO_{10}.H_2O$: C, 65.95; H, 5.03; N, 2.13. Found: C, 66.26; H, 5.15; N, 2.03.

Study of the fraction 7-8 of the column. The combined fractions (212 mg) contained five components which were separated by preparative thin-layer chromatography employing solvent B, double development. The following substances were identified.

Octa-*O*-benzoyl-β-D-glucopyranosyl-(1→1)-α-D-glucopyranoside (octa-*O*-benzoyl-α,β-trehalose (9). This compound (23 mg, 5.3% yield) was obtained as an amorphous powder mp 104-106 °C, $[\alpha]_D$ +43.3° (*c* 0.7, $CHCl_3$). TLC R_F 0.68 (solvent B). ^1H NMR ($DCCl_3$) δ 8.15-7.00 (40 H, benzoyl groups), 6.18 (t, H-3, $J_{2,3}$= $J_{3,4}$ 10 Hz), 5.80 (dd, H-4, $J_{4,5}$ 3.5 Hz), 5.67 (H-1, $J_{1,2}$ 3.6 Hz), 5.65-5.70 (m, H-2', H-3'), 5.75 (H-4', $J_{3',4'}$ 10 Hz), 5.23 (m, H-2, H-1', $J_{1',2'}$ 7.7 Hz), 4.85-4.55 (m, H-5, H-6a, H-6'a, $J_{6a,6b}$ 12.6 Hz, $J_{5,6a}$ 2.7 Hz), 4.38 (H-6b, H-6'b), 4.20 (m, H-5'). FAB+ mass spectrometry M+ 1174.

Anal. Calcd for $C_{68}H_{54}O_{19}$: C, 69.49; H, 4.62. Found: C, 69.20; H. 5.00 .

2,3,4,6-Tetra-*O*-benzoyl-D-glucopyranose (10). A syrupy mixture of anomers was obtained, $[\alpha]_D$ +29.5° (*c* 0.1, $CHCl_3$) (51 mg, 8.5% yield), whose ^{1} H NMR spectrum

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was identical with that of a synthetic sample and also gave a coincident spot on TLC, R_F 0.66 (solvent A), R_F 0.38 (solvent D).

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