The use of iodotrimethylsilane in nucleosidation procedure

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ABSTRACT

1-O-Acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (I) was reacted with iodotrimethylsilane (II) and the product, the glycosyl iodide, was coupled with silylated uracil to afford 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)uracil (III; 89%), with silylated cytosine to afford, on subsequent acetylation, 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4-acetamido-2(1H)-pyrimidinone (IVb; 81%), and with chloromercuri-N-benzoyladenine to afford Va and on subsequent debenzoylation, adenosine (Vb; 49%).

INTRODUCTION

Iodotrimethylsilane is known¹,² to react with alkyl esters under formation of trimethylsilyl esters and alkyl iodides. This fact led us to attempt to prepare a glycosyl iodide by the reaction of a suitably blocked sugar derivative, bearing an anomeric ester³ group, with iodotrimethylsilane and to couple the iodinated product with appropriate pyrimidine or purine bases to obtain the nucleoside derivatives. In contrast to glycosyl chlorides and bromides³,⁴, glycosyl iodides have not been used for the synthesis of nucleosides although they have received considerable attention as reagents for O-glycoside syntheses⁵.

RESULTS AND DISCUSSIONS

1-O-Acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (I) was chosen as the starting sugar component for the reaction with iodotrimethylsilane while uracil, cytosine, and adenine were the used nucleobases. The basic reaction conditions were examined in initial experiments carried out with uracil, It
was found that the desired nucleoside derivative III can be prepared in a "one-pot" process, i.e. when the benzoylated ribose (I) and the silylated uracil are mixed in aprotic solvent (dichloroethane) and iodo(trimethyl)silane is added to the mixture. Using this procedure the yields of III were 75-80%, however, long reaction periods (30-50 h) or heating of the mixture at 70°C for several hours were required in order to complete the nucleosidation reaction. We subsequently found that the reaction proceeds more smoothly and gives higher yields when performed in two steps. Therefore, the reaction of compound I with iodo(trimethyl)silane was performed separately before addition of the silylated base. A molar ratio of 2:1 in the relation of reagent (II) to sugar (I) was found necessary in order to complete the reaction while ratios of 1:1 or 1.5:1 required long reaction times during which side reactions occurred. Under complete exclusion of atmospheric moisture the reaction of I with the iodo reagent II proceeds smoothly in dichloroethane or acetonitrile within several minutes. The product of the reaction, which is homogeneous on TLC, was used immediately, without isolation, for the subsequent nucleosidation reaction with the silylated uracil. As it is known that iodo halogenoses are extremely unstable compounds, we supposed that the spot observed on TLC did not correspond to the iodo halogenose. The end of reaction was therefore indicated indirectly by disappearance of the starting sugar derivative I. The reaction of the thus obtained sugar halogenose with silylated uracil (molar ratio, 1:1.25) in dichloroethane (70°C, 50 min) or acetonitrile (room temperature, 1 h 40 min) afforded the expected compound III in yields of 85% and 89%, respectively (based on starting sugar acetate I).

In the case of cytosine, the procedure was carried out in acetonitrile in a manner similar to the reaction with uracil (40 min, room temperature). In the end, the nucleoside derivative IVa was acetylated to IVb to facilitate the isolation of the product (81%).

In the preparation of a nucleoside from adenine, chloromercuri-N-benzoyladenine was used in the nucleosidation reaction in order to favour the formation of the 9-substituted
In conclusion, this modification of the nucleosidation procedure represents a convenient, preparatively simple alternative route for the preparation of nucleosides. The reaction conditions leave the benzoyl groups unaffected. Also, the method obviates the need for the use of hydrogen chloride or hydrogen bromide for the preparation of the sugar halogenoses. And finally the procedure gives good yields particularly in the pyrimidine series.
Melting points were taken on a heated microscope stage (Kofler block) and are uncorrected. Thin layer chromatography was performed on ready-for-use silica gel sheets Silufol UV \(_{254}\) (Kavalier Glassworks, Votice, Czechoslovakia) in solvent systems \(S_1\), benzene-ethyl acetate 3:1; \(S_2\), ethyl acetate-acetone-ethanol-water 10:1:1:1; \(S_3\), toluene-acetone 3:1. Column chromatography was carried out using Pitra silica gel (particle size, 30-60 \(\mu m\)) produced by Service Laboratories of this Institute in the solvent systems given in the text. All compounds described gave satisfactory elemental analyses. Solutions were concentrated using a rotatory evaporator at 20-40\(^\circ\)C/2.6 kPa. Iodotrimethylsilane was the product of PCR Research Chemicals, Inc., Florida, USA. Acetonitrile was freshly distilled before use. The solvents were stored over Linde molecular sieves (4 Å).

1-(2,3,5-Tri-O-benzoyl-\(\beta\)-D-ribofuranosyl)uracil (III)

A mixture of uracil (280 mg; 2.5 mmol), hexamethyldisilazane (12 ml), and ammonium sulfate (10 mg) was refluxed until the uracil had dissolved (1.5 h) and then for 1 h more. Hexamethyldisilazane was evaporated in vacuo and the residue was coevaporated with toluene (15 ml). In a separate flask, the ribosyl acetate I (1.009 g; 2 mmol) was dissolved in acetonitrile (10 ml), stirred with molecular sieves (1 g) for 15 min, then iodotrimethylsilane (800 mg; 4 mmol) was added and the whole was stirred until the starting material had disappeared (8 min) under formation of a uniform product (TLC, system \(S_1\)). The reaction mixture was transferred to the silylated uracil (dissolved in 7 ml of acetonitrile; 1 g of molecular sieves added) and the whole was stirred at room temperature until the TLC spot of the sugar component disappeared (1 h 40 min). Resulting mixture was evaporated to dryness and the residue was dissolved in chloroform (50 ml). The solution was extracted with 10% solutions of sodium hydrogen carbonate (2x 30 ml) and sodium thiosulfate (2x 30 ml) and with water (30 ml), dried over anhydrous magnesium sulfate, and evaporated in vacuo to afford a foamy product (1.210 g) which was crystallized from
benzene to give chromatographically homogeneous III (814 mg), m.p. 142-144°C (lit. 10, m.p. 142-143°C and lit. 11, m.p. 144-145°C). Column chromatography of the mother liquor on silica gel (22 g, system S1) yielded 176 mg more of III. Total yield, 990 mg (89%). When performed in dichloroethane, the nucleosidation reaction (70°C, 50 min) afforded compound III in 85% yield.

l-(Tri-0-benzoyl-β-D-ribofuranosyl)-4-acetamido-2(1H)-pyrimidinone (IVb)

Cytosine (278 mg; 2.5 mmol) was silylated as described for uracil. The ribosyl acetate I (1.009 g; 2 mmol) in acetonitrile (10 ml) was treated with the reagent II (800 mg; 4 mmol) in the same way as in the preparation of III. The obtained product was allowed to react with the silylated cytosine at room temperature (40 min). The mixture was evaporated to dryness and worked up as described for III. The foamy residue (1.040 g) was acetylated in pyridine-acetic anhydride (15 h, room temperature), the reaction mixture was evaporated to dryness and extracted with chloroform to give, on evaporation, 1.158 g of crude product which was crystallized from ethanol. Yield, 850 mg of IVb, m.p. 188-190°C (reported 12, 191-192°C). Mother liquors afforded additional 120 mg of IVb on chromatography on a silica gel column (22 g) in the system benzene-ethyl acetate 1:1. Total yield, 970 mg (81%).

Adenosine (Vb)

Chloromercuri-N-benzoyladenine9 (300 mg) was stirred in dichloroethane (10 ml) in the presence of molecular sieves (1 g) for 30 min. The ribosyl acetate I (252 mg; 0.5 mmol) in dichloroethane (10 ml) was treated with iodotrimethylsilane (210 mg) as described above. The obtained mixture was allowed to react with the suspension of mercuric salt under stirring at room temperature (30 min) and then at 60°C (10 min). The mixture was worked up as described for III. Chloroform solution of the obtained product was filtered through a column of silica gel (6 g) and evaporated to give 315 mg of chromatographically homogeneous product which was debenzoylated in methanolic ammonia (15 ml, 5 days). Crystallization of the final residue from aqueous methanol afforded 40 mg of adenosine (Vb), m.p. 232.5-
234.5°C (lit., m.p. 234-235°C). Column chromatography of the
mother liquors on silica gel (20 g; system S₂) yielded 25 mg
more of Vb. Total yield, 65 mg (49%). An analogous reaction
in acetonitrile (30 min, room temperature) afforded amorphous
Va in 44% yield on chromatography in the system S₃.

+ Part XXIX in the series Analogues of Nucleosides;
++ The procedure was proposed and initiated by R.A. Earl from
The University of Utah, Salt Lake City during his short
visit (1978) to the Institute of Organic Chemistry and
Biochemistry, Czechoslovak Academy of Sciences under the
auspices of the U.S. National Academy of Sciences and
Czechoslovak Academy of Sciences.
+++ It is known that iodotrimethylsilane also reacts with alkyl
ethers. Therefore, the use of the reaction of alkyl
glycosides with iodotrimethylsilane in nucleosidation
procedure was also examined.

In the course of this work, Gillard and Israel described
the formation of bromo halogenoses by treatment of 1-O-
acetyl sugars with bromotrimethylsilane.

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