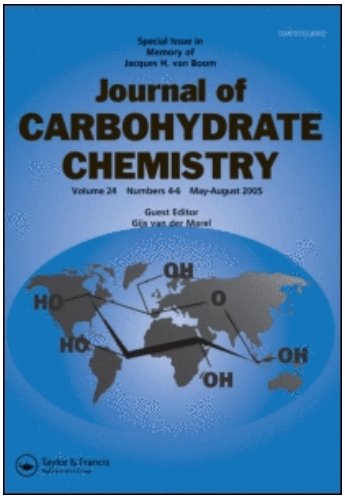

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Thomas W. Flechtner[a]; Helen Pohlid[a]
[a] Department of Chemistry, Cleveland State University, Cleveland, Ohio

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THE INTRODUCTION OF THE DIPHENYLHYDRAZINO SUBSTITUENT BY TRIFLATE DISPLACEMENT. PHOTOCHEMICAL SYNTHESIS OF AN AMINODEOXY SUGAR.

Thomas W. Flechtner* and Helen Pohlid

Department of Chemistry
Cleveland State University
Cleveland, Ohio 44115

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ABSTRACT

The reaction of 1,2:3,4-di-O-isopropylidene-6-O-triflyl-α-D-galactopyranose (4) with N,N-diphenylhydrazine in boiling benzene produced 6-deoxy-1,2:3,4-di-O-isopropylidene-6-(N',N'-diphenylhydrazino)-α-D-galactopyranose (2). The Pyrex-filtered irradiation of 2 in distilled 2-propanol produced 6-amino-6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (5) and carbazole. The results obtained show that, while this procedure is a feasible route for aminodeoxy sugar synthesis, product yields are too low for this synthesis to be of general value.

INTRODUCTION

Aminodeoxy sugar synthesis has been an important area of research for many years.[1] In particular, many procedures have been developed for the replacement of specific hydroxyl groups with amino groups. While

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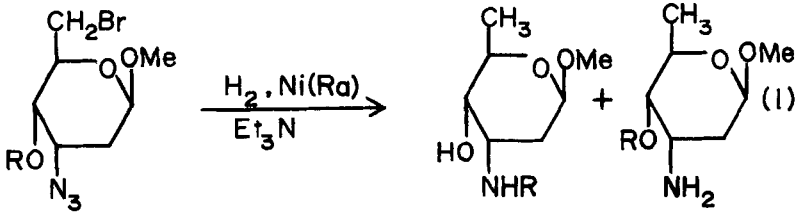
several of these procedures have been shown to be very effective and general, there are exceptional situations in which problems have been reported. For example, using one of the most generally applicable sequences (azide displacement of a sulfonyloxy group followed by reduction of the resulting azidodeoxy sugar) Pelyvas and coworkers[2] observed O to N acyl migration during the reduction step (equation 1).



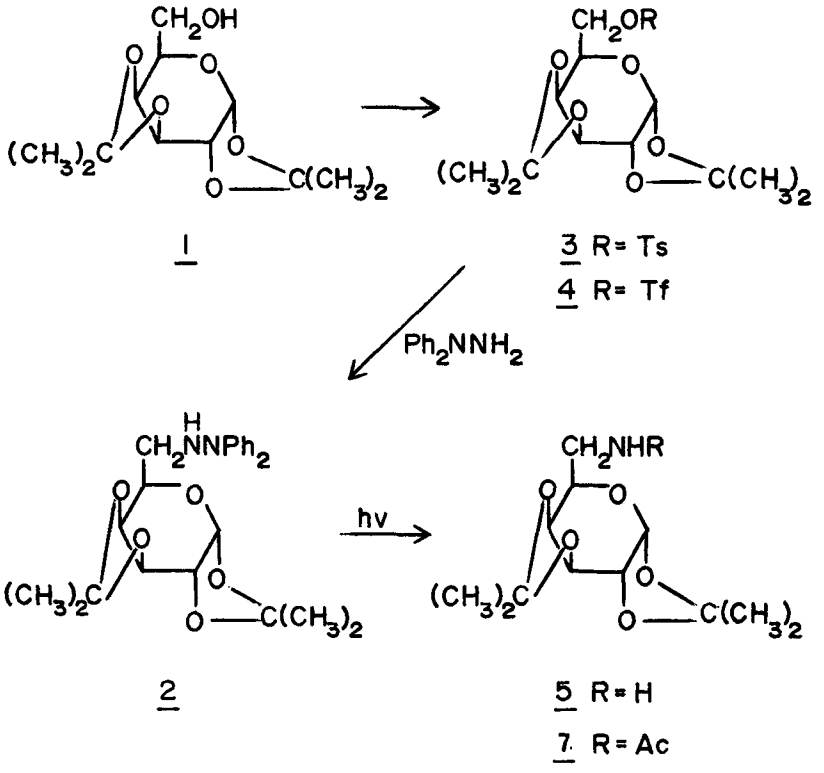
R = COPh

We decided to explore a variation on the "nucleophilic displacement - reduction" sequence in which the reduction step used a photolytic N-N bond cleavage. Our proposal was that the nucleophilic displacement be done using N,N-diphenylhydrazine and that the resulting diphenylhydrazinodeoxy sugar be irradiated in isopropyl alcohol to give the corresponding aminodeoxy sugar. For our initial study we chose 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (1) as the starting material. The reaction sequence is shown in Scheme 1.

RESULTS AND DISCUSSION

Diphenylhydrazine Synthesis

1,1-Diphenylhydrazine was generated from its tosylate salt just before use.[3] This salt was synthesized from diphenylcarbamyl azide[4] by the method of O'Connor and



Scheme 1

Walter.[3] Attempted generation of the free hydrazine directly from the azide by the method of Anselme and Koga[4] afforded, in our hands, a complex mixture of products.

Sulfonate Ester Reaction

Initial attempts to synthesize the desired diphenylhydrazino sugar 2 were made by treating the tosylate 3[5] with diphenylhydrazine. Despite the use of progressively more vigorous conditions (finally 60 h reflux in N,N-dimethylformamide) no evidence (^{1}H NMR) could be obtained for formation of 2. In each case the predominant

components of the reaction mixture were recovered starting materials.

We next turned to the ((trifluoromethyl)sulfonyl)oxy (triflyloxy) leaving group. The reaction of diphenylhydrazine with the sugar triflate (4)[6] also required surprisingly vigorous conditions. After 15 h reflux in benzene under nitrogen and chromatography on Florisil, 2 was otained in 27% yield. The reaction was monitored by ^{1}H NMR. The increase in the relative area of the 6 and 6' hydrogen absorption of 2 was compared with the area of anomeric hydrogen absorption. The relative area of the 6,6' hydrogen absorption ceased to grow when its ratio to that of the anomeric hydrogen was about 1:1 (after 15 h). The maximum yield of 2 before chromatography was about 50%.

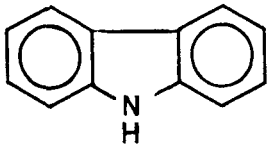
Compound 2 was isolated as a very slightly yellow glass which turned light blue on exposure to air. An acceptable elemental analysis was not obtained but the IR and ^{1}H and ^{13}C NMR spectra were completely consistent with the structure 2. The ^{13}C NMR spectrum showed no extra peaks.

The reluctance of the tosylate 3 to undergo substitution has been previously noted.[7] However, displacements of the tosyloxy group from 3 have been noted often in the literature.[5,6,8] Part of the difficulty here may stem from the weak nucleophilicity of the diphenylhydrazine. The "α effect"[9] should not be important in this compound because of the delocalization of the phenylated nitrogen atom's non-bonding electrons. The electronegativity of this nitrogen atom should then make the NH_2 group less nucleophilic than ammonia.[8]

Hydrazino Sugar Photolysis.

Compound 2 was irradiated for 2 h with Pyrex-filtered light in dry deoxygenated isopropanol containing sodium bicarbonate. The brown syrup which was obtained after

filtration and solvent removal had a ^{1}H NMR spectrum in which the region upfield from δ6.6 was similar to that of the expected aminodeoxy sugar 5[5] while that part of the spectrum downfield from δ6.6 was essentially superimposable on the spectrum of carbazole (6).



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The photoproduct mixture was slurried with chloroform and filtered. The solid was identified as carbazole.

Previous experience had indicated that the aminodeoxy sugar 5 would be troublesome to purify so the chloroform-soluble material was acetylated using a standard procedure.[5] After preparative TLC purification the acetamido sugar 7 was isolated in 27% yield. The material obtained in this way had ^{1}H and ^{13}C NMR spectra superimposable on those of material prepared by a classical[5] route. The ^{13}C NMR spectra of 7, 1, and 2 with assignments are presented in Table 1.

A proposed mechanism for the photochemical reaction is shown in Scheme 2. The N-N bond cleavage and subsequent hydrogen-atom abstraction by the resulting radicals have ample precedent[10] and will not be discussed further. The photochemical reaction of diphenylamine to produce carbazole has been previously reported[11] and this may account for the presence of carbazole in the reaction product mixture. A significant amount of diphenylamine may have been formed in the reaction although it was not detected. The cyclization may also have occurred at an earlier stage in the reaction process. No effort was made to determine whether diphenylamine does indeed

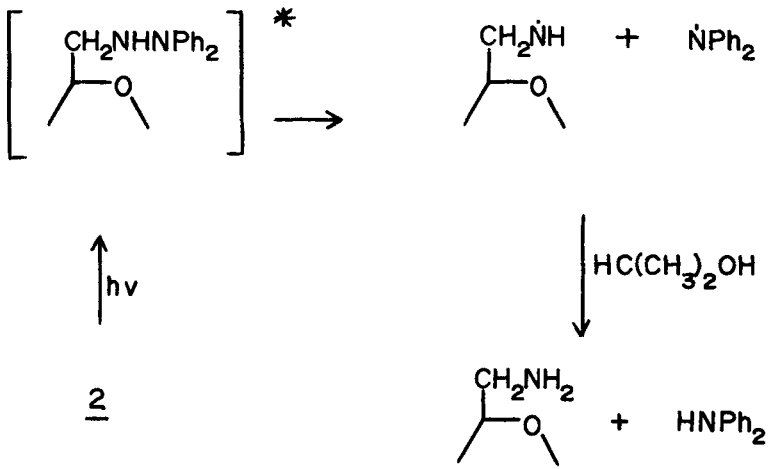
TABLE 1

^{13}C NMR Spectra[a] of 1, 2, and 7

Assignment[b]	1	2	7
C-1	96.3	96.3	95.8
C-2,C-3,C-4	71.5,70.8, 70.6	72.0,70.7, 70.5	71.2,70.3, 70.1
C-5	68.4	65.8	65.9
C-6	62.1	48.9	39.6
$(CH_3)_2\underline{C}$	109.5,108.7	109.0,108.4	108.8,108.3
$(\underline{C}H_3)_2C$	26.0(2), 25.0,24.4	25.8,25.7, 24.8,24.4	25.5(2), 24.5,23.9
Other		147.3,129.4, 128.8,122.2 122.0,120.2 (Aromatic)	22.5($\underline{C}H_3C(O)$) 170.5($CH_3\underline{C}(O)$)

[a]Reported in parts per million downfield from internal tetramethylsilane with $CDCl_3$ as solvent.

[b]Assignments within any group separated by commas are arbitrary.



Scheme 2

cyclize under our conditions to form carbazole; the conditions necessary for the photocyclization reported[11] are similar to those used here. In addition, the photochemistry of the compound which would result from cyclization without N-N bond cleavage was not investigated.

The low chemical yield obtained in the photochemical step must have been caused, in part, by the processes used for product isolation. The desired reaction, however, is only one of the many possible[12] and this probably is the major cause of the low yield. In addition, the carbazole formed in the reaction must absorb an increasing portion of the light as the reaction proceeds.

The results obtained in this work were sufficiently discouraging that no attempt was made to maximize the yields of the individual steps.

EXPERIMENTAL

General Procedures. ^{1}H NMR spectra were obtained using either a Varian T-60 spectrometer or a Varian FT-80 spectrometer. ^{13}C NMR spectra were determined using the Varian FT-80 instrument.

Attempted Preparation of 6-Deoxy-1,2:3,4-di-O-isopropylidene-6-(N',N'-diphenylhydrazino)-α-D-galactopyranose (2) by Tosylate Displacement. 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose (1) and the 6-O-tosylate 3 were prepared by the methods of Raymond and Schroeder.[13] Compound 3 was heated in various solvents (benzene, xylene and dimethylformamide) with N,N-diphenylhydrazine[3] for various periods. In each case the ^{1}H NMR spectrum of the reaction mixture after solvent removal showed no absorption in the region (~δ2.9) where H-6 and H-6' absorption for the desired product was expected. In each case the ^{1}H NMR spectrum of the product mixture was essentially superimposable on the spectrum of the reactant mixture.

The last such attempt is given as an example. A mixture of 226 mg (0.545 mmol) of 3 and 225 mg (1.24 mmol) of N,N-diphenylhydrazine[3,4] in 25 mL of dimethylformamide was heated at reflux under a nitrogen atmosphere for 60 h. The ^{1}H NMR spectrum of the reaction mixture (472 mg) after solvent removal *in vacuo* indicated only unreacted starting materials.

Preparation of 6-Deoxy-1,2:3,4-di-O-isopropylidene-6-(N',N'-diphenylhydrazino)-α-D-galactopyranose (2) by Triflate Displacement. The triflate 4 was prepared as described previously.[8] Compound 4 (3.95 g, 10.1 mmol) and N,N-diphenylhydrazine (1.85 g, 10.1 mmol) in 100 mL of dry benzene were heated at reflux. Aliquots (1 mL) were removed at times of 0, 10, 12, and 15 h. From each aliquot the solvent was removed and the ^{1}H NMR spectrum recorded. In each case the integral of the absorption assigned to the anomeric hydrogen (at δ5.32) was compared to that assigned to H-6,6' of 2 (at δ2.90). In the 15 h aliquot the relative absorption intensity at δ2.90 was the same as in the 12 hr sample. The ratio of the two signals was 1:1.

The reaction mixture was then cooled, the solvent removed *in vacuo* and the resulting brown syrup (5.23 g) was chromatographed on a 1 m x 5 cm column slurry-packed with Florisil (J. T. Baker) in hexane. The column eluant absorption at 254 nm was monitored and 50 mL fractions were collected. The column was eluted first with 1 L of 10% diethyl ether in hexane and then 1 L of 20% ether in hexane. Fractions 40-55 afforded 2 as a pale yellow syrup; 1.157 g (27%). ^{1}H NMR spectrum: 7.03 (10H, aromatic), 5.32 (1H, J=5 Hz, H-1), 4.68-3.85 (5H, H-2,3,4,5, N-H), 2.90 (2H, broadened doublet with a principle coupling of *ca*. 5 Hz, H-6,6'), 1.42, 1.35 (12H, CMe_2). The ^{13}C NMR spectrum is given in Table 1.

Irradiation of 2 and Isolation of 6-Acetamido-6-Deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (7). Nitrogen was bubbled for 1 h through a solution of 701 mg (1.63 mmol) of 2 in 330 mL of dry isopropyl alcohol containing 200 mg (2.4 mmol) of $NaHCO_3$. The nitrogen flow was continued while this solution was irradiated with light from a 450-W Hanovia medium pressure, mercury vapor lamp in a quartz immersion well using a Pyrex filter for 2 h. This slurry was then filtered and the solvent removed *in vacuo* to afford 650 mg of brown syrup. This material was slurried with chloroform and filtered twice to afford 103 mg of a solid whose ^1H NMR spectrum was superimposable on that of carbazole (6). The chloroform-soluble material was dissolved in 10 mL of freshly-distilled acetic anhydride, 1.80 g of fused sodium acetate was added; and this mixture was stirred at room temperature for 12 h. It was then poured into 100 mL of water and stirred for 1 h. The resulting mixture was extracted two times with 50 mL portions of ether. The combined ether extracts were dried over sodium sulfate and the solvent removed *in vacuo* to afford 325 mg of a brown glass. This material was chromatographed on two 20 x 20 cm preparative TLC plates (silica gel 60 F 254, 2 mm thickness). The plates were developed three times using 20% methanol in ether. The band which migrated the same as the material prepared by another route[5] afforded 132 mg (0.438 mmol, 27% yield from 2) of material whose ^1H and ^{13}C (see Table 1) NMR spectra were superimposable on those of the authentic material.[5]

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REFERENCES AND FOOTNOTES

1. a) D. Horton, in "The Amino Sugars," R. W. Jeanloz, ed., Academic Press, Inc., New York, N.Y., 1969, Vol. 1A, p. 3. b) S. Hanessian and T. H. Haskell, in "The Carbohydrates; Chemistry and Biochemistry," W. Pigman and D. Horton, eds., Academic Press, Inc., New York, N.Y., 2nd Edition, 1970, Vol. IIA, p. 159. c) S. Umezawa, Adv. Carb. Chem. Biochem., 30, 111 (1974). d) K. L. Rinehart, Jr. and T. Suami, "Aminocyclitol Antibiotics," American Chemical Society, Washington, D. C., 1980.

2. I. Pelyvas, F. Sztaricskai, L. Szilagyi, R. Bognar and J. Tamas, Carbohydr. Res., 68, 321 (1979).

3. S. E. O'Connor and R. I. Walter, J. Org. Chem., 42, 577 (1977).

4. J.-P. Anselme and N. Koga, J. Org. Chem., 33, 3963, (1968).

5. W. A. Szarek, and J. K. N. Jones, Can. J. Chem., 43, 2345 (1965).

6. a) L. D. Hall and D. C. Miller, Carbohydr. Res., 47, 299 (1976); b) R. W. Binkley and D. G. Hehemann, J. Org. Chem., 43, 3244 (1978).

7. S. Nadkarni and N. R. Williams, J. Chem. Soc., 3496, (1965).

8. T. W. Flechtner, Carbohydr. Res., 77, 262 (1979).

9. N. J. Fina and J. O. Edwards, Int. J. Chem. Kinet., 5, 1 (1973).

10. G. N. Lewis and D. P. Lipkin, J. Am. Chem. Soc., 64, 2801 (1942); P. F. Holt and B. P. Hughes, J. Chem. Soc., 98 (1954); R. W. Binkley, J. Org. Chem., 33, 2311 (1968); D. G. Horne and R. G. W. Norrish, Proc. Roy. Soc., Ser A, 315, 301 (1970).

11. H. Linschitz and K. H. Grellman, J. Am. Chem. Soc., 86, 303 (1964).

12. E. W. Forster, K. H. Grellman, and H. Linschitz, J. Am. Chem. Soc., 95, 3108 (1973).

13. A. L. Raymond and E. F. Schroeder, J. Am. Chem. Soc., 70, 2785 (1948).