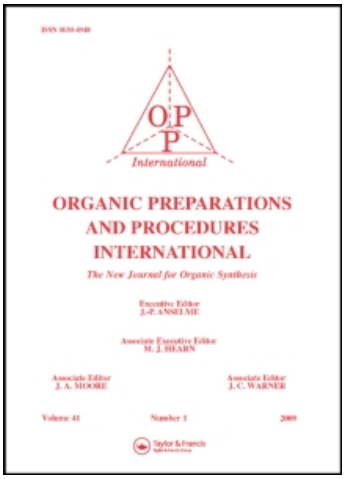

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IMPROVED PREPARATION OF METHYL 4,6-O-BENZYLIDENE-α-D-GLUCOPYRANOSIDE

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IMPROVED PREPARATION OF METHYL 4,6-O-BENZYLIDENE-α-D-GLUCOPYRANOSIDE

Submitted by (02/22/99)

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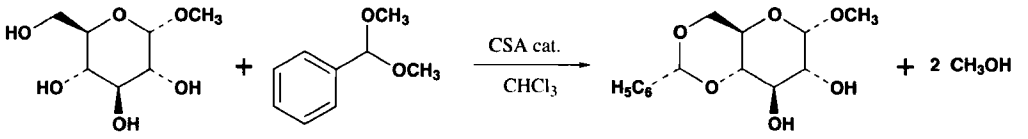
Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside is one of the most widely used monosaccharide derivatives. The use of a benzylidene acetal as a protecting group has several advantages, in terms of stability, conformational rigidity and selective cleavage, amongst others.[1] There are several methods for preparing this monoprotected derivative.[2] A commonly used procedure[3] employs a *trans* acetalation reaction of methyl-α-D-glucopyranoside with benzaldehyde diethyl acetal, carried out in chloroform under reflux with camphorsulfonic acid as catalyst. The product is obtained in good yield. However, on a large scale, the reversibility of the process becomes evident; it does not reach completion unless the ethanol generated is continuously removed by codistillation and a constant reaction volume must be maintained by the addition of fresh chloroform.

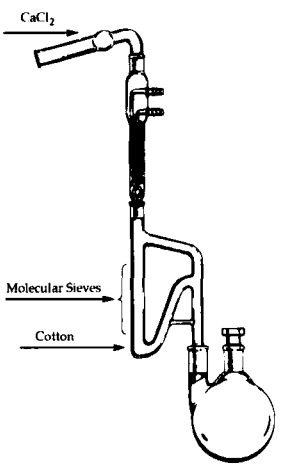


In order to avoid this problem, we used benzaldehyde dimethyl acetal and 4 Å molecular sieves to remove the methanol liberated and any trace of water. To accomplish this purpose, we adapted a Dean Stark trap for solvents heavier than water to a two-neck round bottom flask with a small piece of cotton placed at the bottom of the trap reservoir and loaded with molecular sieves (Figure). In this way, the methanol could be removed from the reaction mixture by forcing the refluxing solvent to pass through the molecular sieves column before returning to the reaction vessel and the reaction equilibrium could be displaced completely toward the product. This procedure proved to be very effective; the reaction was complete in 6 hours. In a parallel experiment using the same quantities of reagents but without the molecular trap, a considerable amount of starting material was detected by TLC even after 36 hours of reflux.

This modification makes the procedure much simpler and adds no extra cost because molecular sieves are easily regenerated since they are only in contact with distilled solvents. Furthermore, what is more important, the method becomes more environmentally friendly by minimizing the use of ecologically harmful chlorinated solvent.

EXPERIMENTAL SECTION

Melting points were taken on a Leitz Wetzlar Microscope Heating Stage Model 350 apparatus and are uncorrected. All reactions were monitored by thin layer chromatography carried out on 0.25 mm E. Merck silica gel plates ($60F_{254}$) using UV light and anisaldehyde-sulfuric acid as developing agent. Optical rotations were measured on a Jasco DIP–1000 digital polarimeter. Methyl-α-D-glucopyranoside was purchased from Aldrich Chemical Company, camphor-10-sulfonic acid monohydrate was obtained from Fluka and both reagents were used as received. Benzaldehyde dimethyl acetal was prepared according to the literature procedure.[4]



Procedure.- The benzylidene dimethyl acetal (5.4 mL, 36 mmol) was dissolved in chloroform (130 mL) and camphorsulfonic acid monohydrate (0.2 g, 0.86 mmol) and methyl-α-D-glucopyranoside (5 g, 25.7 mmol) were sequentially added. A Dean Stark trap for solvents heavier than water and loaded with 4 Å molecular sieves (8.2 g) (activated at 350° for 3 h.) was fitted into the flask and the reaction mixture was stirred and heated at reflux during 6 h. The reaction progress was monitored by TLC and quenched by adding potassium carbonate (1 g), maintaining the stirring and heating for an additional period of 0.5 h. Filtration of the hot solution through a filter funnel with a porosity E sintered glass fritted disc and evaporation of the solvent under vacuum from the filtrate afforded a white solid which was washed thoroughly with petroleum ether (to remove excess reagent). The crude solid was recrystallized from isopropyl alcohol yielding pure methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (6.06 g, 83%) as white needles, mp. 167-168°, $[\alpha]_D^{25}$ +110 (c = 2, chloroform), lit: mp. 163-164°, $[\alpha]_D^{20}$ +113;[3] mp. 166-167°, $[\alpha]_D$ +105 (C = 1.1, chloroform);[4] mp. 160-162°, $[\alpha]_D$ +80 (water);[5] mp. 163-164°, $[\alpha]_D^{20}$ +110 (C = 2, chloroform);[6] mp. 166-167°, $[\alpha]_D^{25}$ +108 (C=2, chloroform).[7]

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A NEW AND EFFICIENT SOLVENT-FREE SYNTHESIS OF *bis*-ARYL CARBODIAZONES

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Azo compounds are very important in organic chemistry. Recently many studies have shown that they are also widely utilized in modern technology.[1] There is continued interest in efficient syntheses of new types of azo compounds in our laboratory. As a result, several methods for preparing new azo compounds in which one side of the –N=N- is connected with a carbonyl group have been reported.[2-5] All the useful synthetic routes available for the solution-state synthesis have their own merits, but some have drawbacks such as expensive phase-transfer catalysts,[2] large amounts of solvent,[3] tedious work to prepare the oxidant system[4] and complicated heating and stirring apparatus.[5] In the last few years, particularly intense interest has been directed towards methods for generating small organic molecules by solid-phase reactions. These solvent-free reactions are especially appealing for their own advantages including ease of set-up, work-up, high yields and working with open vessels. A variety of classical reactions have been adapted to solid-phase synthesis to generate C=C[6] and C=O[7-8] bonds. By comparison, the formation of N=N bonds remains relatively unexplored. This has led us to investigate the synthesis of azo compounds. As an improvement to our previous work,[2-5] we now report an effective solid-phase method for the rapid oxidation of aryl substituted carbohydrazides to the corresponding bisaryl carbodiazones [$(ArN{=}N)_2CO$], using $Fe(NO_3)_3{\bullet}9H_2O$ as oxidant. All the reactions occurred under mild conditions and yields were fair to excellent.

Our work started with the choice of oxidant. Several oxidants were attempted with the following results: **(a)** CrO_3-Al_2O_3 can react easily with aryl substituted carbohydrazides (judging from the color change of the reactants), but none of the expected product was obtained. **(b)** $Fe_2(SO_4)_3{\bullet}10H_2O$ can lead to the formation of bisazo compounds at room temperature, but the yields were seldom above 60%. **(c)** $Cu(NO_3)_2{\bullet}3H_2O$ gave similar results as $Fe_2(SO_4)_3{\bullet}10H_2O$ but with lower yields. Finally, we found $Fe(NO_3)_3{\bullet}9H_2O$, a low cost and highly stable commercially available crys-