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A NEW METHOD FOR GLYCOSYLATION WITH CARBODIIMIDES; NUCLEOPHILIC SUBSTITUTION OF GLYCOSYLISOUREAS[1]

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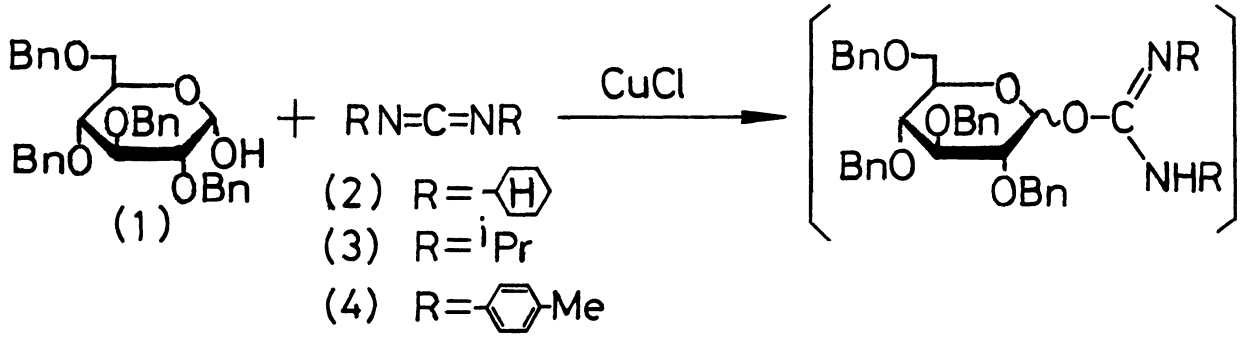
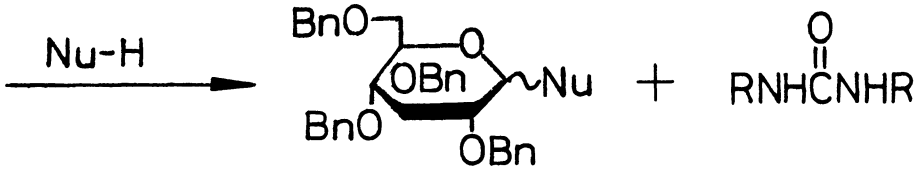
A glycosyl isourea, prepared from a sugar derivative with free 1-hydroxyl group and a carbodiimide in the presence of cuprous chloride, was successfully subjected to the reaction with a series of protic nucleophiles to give the corresponding glycosyl compounds, i.e., 1-O-acylglycoses, phenyl glycosides, alkyl glycosides including disaccharides, and purine nucleosides, in good yields.

Glycosylation reaction of a nucleophile has been effected by use of glycosyl halide derivatives[2,3], sugar 1,2-orthoesters[2], sugar 1-acetates[4], sugar 1-carbonates[5], sugar 1-sulfonates[6], and sugar 1-(N-methyl)acetimidates[7], and by transglycosidation[8]. On the other hand, the nucleophiles have been activated by metallation[9] and silylation[10] etc. In the course of our investigation on the reaction, we have been interested in the chemistry of carbodiimides; carbodiimides have been shown to condense with alcohols in the presence of cuprous chloride etc. as the catalyst to give the corresponding isourea derivatives[11], and the resulting isoureas are synthetically useful intermediates for subsequent nucleophilic substitution reaction[12,13]. Moreover, carbodiimidium iodides have been used for conversion of alcohols into the corresponding alkyl iodides[14]. On the other hand, dicyclohexylcarbodiimide (DCCI) has been reported to cause the isomerization of D-fructose, on refluxing in methanol, into a mixture containing D-glucose, D-mannose, and D-psicose[15]. Such aspects of the chemistry prompted us to investigate the substitution reaction of glycosylisourea derivatives with some species of nucleophiles in view of potential utility of the reaction for the synthesis of glycosyl compounds and/or C-1 substituted glycoses. 2,3,4,6-Tetra-O-benzyl-α-D-

glucopyranose (1)[16] was used as the "model" sugar for the sake of making the products easy to isolate after the reaction.





Bn=-CH_2Ph
Nu-H ; nucleophile

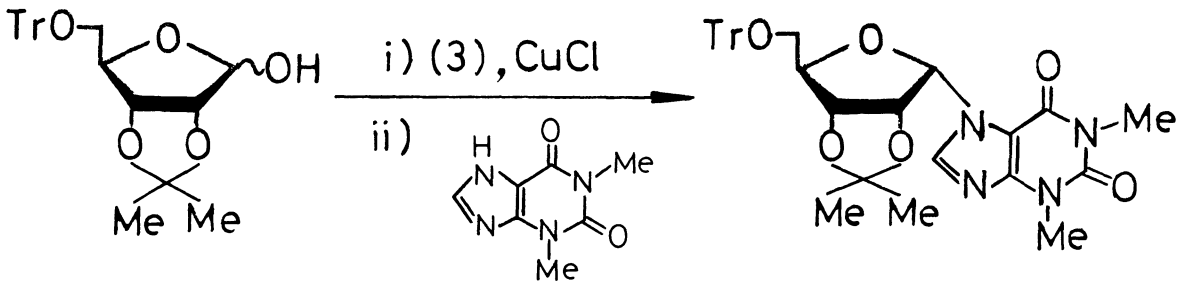
Fusion of a mixture of (1)(2 mmol) and DCCI (2)(6 mmol) in the presence of cuprous chloride (0.02 mmol) at 80 – 85°C for 0.5 h, followed by reaction with p-methoxyphenol (6 mmol) at 80 – 85°C for 1 h, gave p-methoxyphenyl 2,3,4,6-tetra-O-benzyl-D-glucopyranosides (93% yield; α:β = 17:83[17]); crystallization from methanol gave the β-anomer (77% yield). A similar reaction with thiophenol in place of p-methoxyphenol gave the corresponding β-anomer (83% yield).

The glycosylisourea, prepared by the above first step, gave the 1-O-acetyl derivatives (88% yield; α:β = 12:88[17]), on stirring with 1M aqueous acetic acid solution at 0°C for 2 h in methylene dichloride. N-Benzyloxycarbonylglycine gave the corresponding β-anomer (31% isolated-yield) in a similar reaction.

As for the reaction with alcohols, the glycosylisourea prepared from (1) and (2) was first dissolved in benzene and extracted with 1M aqueous ammonia to wash out the catalyst. The resulting syrup obtained by evaporation of the organic layer (dried over Na_2SO_4) was then subjected to the reaction with alcohols (2 ml). The reaction with methanol under reflux for 10 h gave methyl 2,3,4,6-tetra-O-benzyl-α- (55% yield) and -β-D-glucopyranoside (22% yield). tert-Butyl alcohol

similarly gave the corresponding glucopyranosides (54% yield; α > 95%[17]). There has been observed no difference in the yields and the anomeric proportions on utilization of diisopropyl- (3) and di-p-tolylcarbodiimide (4) to these reactions. Extention of this procedure to disaccharide formation has been similarly attained; the glycosylisourea was prepared by treating a mixture of (1)(2 mmol), (3)(2 mmol), and cuprous chloride (0.02 mmol) in chloroform (2 ml) at room temperature for 24 h, and, after the removal of the catalyst, the reaction with 1,2;5,6-di-O-isopropylidene-α-D-glucofuranose (2 mmol) was performed in benzene under reflux for 40 h. The corresponding disaccharides with α- and β-anomeric configuration were obtained in 25% and 19% yields, respectively. Similar reactions with methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside and methyl 2,3-O-isopropylidene-β-D-ribofuranoside gave the corresponding disaccharides in 55% (α:β = 77:23[17]) and 62% (α:β = 79:21[17]) yields, respectively.

Moreover, synthesis of a nucleoside has similarly been performed by treating the glycosylisourea with theophylline (2 mmol) in chloroform at room temperature for 24 h, giving the corresponding nucleosides with β- and α-configuration in 63%



and 17% yields, respectively. Confronting with this result, we attempted the reaction by use of 2,3-O-isopropylidene-5-O-trityl-D-ribofuranose in place of (1) in a similar manner, giving the corresponding α-nucleoside in 60% yield {$[\alpha]_D$ -32° (c 1.0, $CHCl_3$); δ($CDCl_3$-TMS): 6.98 (H-1', $J_{1',2'}$ = 5 Hz)[18]}. Therefore, this procedure is of great interest from the viewpoint of synthesizing a sereis of α-ribonucleosides in parallel with that involving a boron trichloride-catalyzed coupling reaction of methyl D-ribofuranoside with a purine[19].

The structures of the products obtained here were confirmed through elemental analysis, and IR and ^1H- and ^{13}C-NMR spectroscopy.

Detailed investigation on these reactions is now in progress in connection with each series of the nucleophiles as well as the steric course of the reactions resulting in the variety of the anomeric proportions observed herein.

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17) These anomeric proportions were determined through ^{13}C-NMR spectroscopy.
18) The corresponding β-anomer derived from 7-(2,3-O-isopropylidene-β-D-ribofuranosyl)theophylline by usual tritylation had $[\alpha]_D$ +20°(c 1.0, $CHCl_3$); δ($CDCl_3$-TMS): 6.17 (H-1', $J_{1',2'}$ = 3 Hz).
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