Carbohydrate Research, 88 (1981) 61–75
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

SYNTHESIS OF PHENYL D-GLUCOPYRANOSIDES; NUCLEOPHILIC SUBSTITUTION OF *O*-(2,3,4,6-TETRA-*O*-BENZYL-D-GLUCOPYRANOSYL)-PSEUDOUREAS BY PHENOLS*

HIDEO TSUTSUMI AND YOSHIHARU ISHIDO
Department of Chemistry, Faculty of Science, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152 (Japan)

(Received June 12th, 1980; accepted for publication, July 23rd, 1980)

ABSTRACT

A series of nucleophilic substitution-reactions of *O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)pseudoureas by phenols was investigated as a novel procedure for the synthesis of phenyl D-glucopyranoside derivatives: these reactions were found to give the corresponding phenyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosides in excellent yields. Reaction mechanisms were discussed on the basis of the results obtained.

INTRODUCTION

Carbodiimides have been widely used as excellent dehydrating agents for the synthesis of amides, esters, and ethers in the field of organic chemistry[2–4]. In particular, Bach[5] and Vowinkel[6] reported in detail the condensation of phenols with alcohols, leading to the corresponding ethers. The reaction was explained as involving, first, formation of the corresponding *O*-alkylpseudourea from an alcohol and a carbodiimide, and then, subjection of the pseudourea thus formed to nucleophilic attack by the phenol through an SN2 reaction, to afford the corresponding alkyl phenyl ether and urea derivative, but the alcohols used were all achiral. Therefore, it was desirable that the steric course of the reaction should be further investigated by use of chiral alcohols, in order to make the discussion unambiguous.

In addition, *O*-alkylpseudourea derivatives are readily prepared by the copper(I)-catalyzed reaction of an alcohol with a carbodiimide[7]: this reaction should also be feasible for a protected sugar derivative having a free hydroxyl group on the anomeric carbon atom; this hydroxyl group is more reactive than others, and the resulting pseudourea should be far more nucleofugal than the corresponding, ordinary *O*-alkylpseudoureas. On the basis of such an assumption, we have successfully established a novel glycosylation reaction that has already been communicated briefly[8]. We now report some of the details involved in the synthesis of a series of substituted-phenyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosides.

*Partial Protection of Carbohydrate Derivatives. Part V. For Part IV, see ref. 1.

RESULTS AND DISCUSSION

It is well known that, in conventional glycosylation reactions, glycosylating agents bearing *O*-acyl groups vicinal to the anomeric center give the corresponding 1,2-*trans*-glycosyl compounds, or 1,2-orthoester derivatives, or both[9]. In order to confine the products to the glycosidic species by avoiding such anchimeric effects, we used 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose[10] (**1**), having an established anomeric configuration, thus facilitating discussion of the stereochemical aspect of the reaction mechanism involved.

Fusion procedure. — Conditions for the D-glucosylation reaction were examined by use of the model compounds **1**, dicyclohexylcarbodiimide (**2**), and *p*-methoxyphenol (**6**). In light of the application to ether formation[5,6], **1** (2.0 mmol), **2** (2.0 mmol), and **6** (2.0 mmol) were cofused (Procedure 1). The fusion was also conducted in the presence of a catalytic amount of copper(I) chloride (Procedure 2). For comparison, a two-stage reaction (Procedure 3) was performed, namely, fusion of **1** (2.0 mmol) and **2** (2.0 mmol) in the presence of the catalyst (0.02 mmol), followed by reaction with **6** (2.0 mmol). The results thus obtained are summarized in Table I.

Performance of Procedure 1, followed by chromatographic separation of the resulting mixture on a column of silica gel, gave a mixture of *p*-methoxyphenyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosides (**22**) ($\alpha:\beta$ = 59:41) in only 16% yield. Because Däbritz[11] had reported that coordination of one of the nitrogen atoms of carbodiimides to copper(I) ion makes its central carbon atom more positively charged, thus facilitating the nucleophilic attack of alcohols, Procedure 2 was examined, and the yield of **22** was raised to 29% ($\alpha:\beta$ = 14:11). In addition, Procedure 3 was performed, to give **22** (unexpectedly, $\alpha:\beta$ = 3:17) in 45% yield. These results

TABLE I

COMPARATIVE EXAMINATION OF PROCEDURES 1, 2, AND 3 IN SYNTHESIS OF 22

Procedure	*Reaction conditions*[a]	*Yield (%)*		
		22	$\alpha:\beta$[b]	**1**
1	**1** —(**2**, **6**; 3 h, 80–85°)→ **22**	16	[59:41]	73
2	**1** —(**2**, **6**, CuCl; 1.5 h, 80–85°)→ **22**	29	[56:44]	54
3	**1** —(**2**, CuCl; 0.5 h, 80–85°)→ —(**6**; 1 h, 80–85°)→ **22**	45	[15:85]	43

[a]In all of the reactions, **1** (2.0 mmol), **2** (2.0 mmol), **6** (2.0 mmol), and CuCl (0.02 mmol; unless otherwise noted) were used. [b]These ratios were calculated in terms of the area-ratios of the C-1 signals at δ 96.5 (α anomer) and 102.8 (β anomer) in the ^{13}C-n.m.r. spectra.

TABLE II

EXAMINATION OF REACTION CONDITIONS IN FUSION REACTION OF **1** WITH **6**

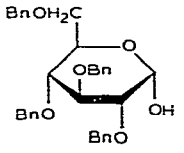
Entry	*Reagent (mmol)*				*Reaction conditions*		*Yield (%) of*		
	1	**2**	*CuCl*	**6**	*Temp. (°C) and time (min)*		**22**	[α:β[a] β[b]]	**1** *(recovered)*
					First stage	*Second stage*			
1	2.0	6.0	0.02	2.0	50–55, 90	50–55, 90	73	[N.d.[c] 48]	18
2	2.0	6.0	0.02	6.0	50–55, 90	50–55, 90	87	[11:89 N.d.]	5
3	2.0	2.0	0.02	2.0	80–85, 30	80–85, 60	45	[15:85 28]	43
4	2.0	4.0	0.02	4.0	80–85, 30	80–85, 60	81	[N.d. 67]	18
5	2.0	6.0	0.02	6.0	80–85, 30	80–85, 60	93	[17:83 77]	2
6[d]	2.0	6.0	0.02	6.0	80–85, 30	80–85, 60	85	[19:81 64]	9
7	2.0	6.0	0.02	6.0	80–85, 15	80–85, 30	67	[17:83 53]	18
8	2.0	6.0	0.02	6.0	120–125, 5	120–125, 10	91	[20:80 69]	3

[a]These proportions were calculated in terms of the area-ratios of the C-1 signals at δ 96.5 (α anomer) and 102.8 (β anomer) in the ^{13}C-n.m.r. spectra. [b]These yields were of **22** crystallized from methanol. [c]N.d. = Not determined. [d]In this case, CuCl was removed after the first-stage reaction.

indicated that the steric course of the reaction differs for Procedures 1, 2, and 3, and that the last is superior in stereoselectivity, giving mainly the β anomer. Procedure 3 is, therefore, promising as a new glycosylation reaction, judging from the simple procedure and mild conditions, in addition to the excellent stereoselectivity. The compound **1** that may be recovered consists of unreacted material (in the first stage) and that from the hydrolyzate of the unreacted 1,3-dicyclohexyl-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)pseudourea (**50**) in the second stage.

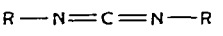
Consequently, we further investigated, in detail, the conditions for the reaction, *i.e.*, the temperature, the reaction time, and the molar proportions of the reagents, in order to improve the yield of **22**; the results thus obtained are summarized in Table II (Entries 1–8). To **1** (2.0 mmol) and copper(I) chloride (0.02 mmol) were added 2, 4, and 6 mmol of **2** in the first stage (30 min at 80–85°), and 2, 4, and 6 mmol of **6** in the second stage (60 min at 80–85°) (see Entries 3–5). The yield of **22** was expectedly improved from 45 to 81, and then to 93% in these reactions. Performance of the second stage after washing out the catalyst with aqueous ammoniacal solution (Entry 6) produced essentially the same result. As may be seen from Entries 1, 2 (50–55°), and 8 (120–125°), compound **22** was obtained in satisfactory yields regardless of whether the reaction time was long or short, taking the temperature into consideration. If the amount of catalyst was increased to 0.2 mmol, however, the reaction mixture was undesirably discolored, even though the reaction time was shortened, giving **22** and **1** in lower yields (Entry 7); thin-layer chromatography (t.l.c.) of the resulting mixture afforded many spots of by-products arising from side reactions.

In the light of the best conditions found (Entry 5, Table I), a series of D-glucosylation reactions of phenols (**6–21**) was performed by use of **1**, the catalyst

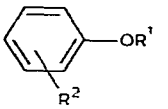


1

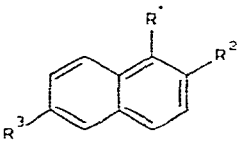
Bn = $-CH_2Ph$



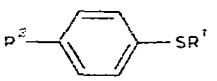
2 R = $-C_6H_{11}$
3 R = $-CHMe_2$
4 R = $-C_6H_4Me$-*p*
5 R = $-C_6H_4Me$-*o*



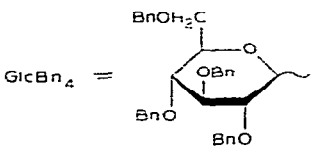
	R^1	R^2		R^1	R^2
6	— H	— OMe-*p*	22	— $GlcBn_4$	— OMe-*p*
7	— H	— H	23	— $GlcBn_4$	— H
8	— H	— NO_2-*p*	24	— $GlcBn_4$	— NO_2-*p*
9	— H	— NO_2-*m*	25	— $GlcBn_4$	— NO_2-*m*
10	— H	— NO_2-*o*	26	— $GlcBn_4$	— NO_2-*o*
11	— H	— Me-*p*	27	— $GlcBn_4$	— Me-*p*
12	— H	— Me-*m*	28	— $GlcBn_4$	— Me-*m*
13	— H	— Me-*o*	29	— $GlcBn_4$	— Me-*o*
14	— H	— Cl-*p*	30	— $GlcBn_4$	— Cl-*p*
15	— H	— Cl-*m*	31	— $GlcBn_4$	— Cl-*m*
16	— H	— Cl-*o*	32	— $GlcBn_4$	— Cl-*o*
17	— H	— CN-*p*	33	— $GlcBn_4$	— CN-*p*
18	— H	— CN-*o*	34	— $GlcBn_4$	— CN-*o*
19	— H	— CHO-*p*	35	— $GlcBn_4$	— CHO-*p*
20	— H	— CHO-*o*	36	— $GlcBn_4$	— CHO-*o*
21	— H	— CO_2Me-*o*	37	— $GlcBn_4$	— CO_2Me-*o*

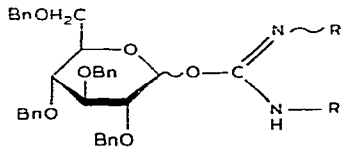


	R^1	R^2	R^3		R^1	R^2	R^3
38	— OH	— H	— H	42	— $OGlcBn_4$	— H	— H
39	— H	— OH	— H	43	— H	— $OGlcBn_4$	— H
40	— NO_2	— OH	— H	44	— NO_2	— $OGlcBn_4$	— H
41	— NO_2	— OH	— NO_2	45	— NO_2	— $OGlcBn_4$	— NO_2

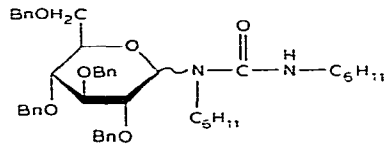


	R^1	R^2		R^1	R^2
46	— H	— H	48	— $GlcBn_4$	— H
47	— H	— Cl	49	— $GlcBn_4$	— Cl

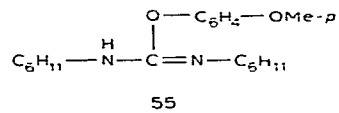




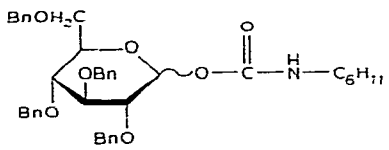
50 R = $-C_6H_{11}$
51 R = $-CHMe_2$
52 R = $-C_6H_4Me$-*p*
53 R = $-C_6H_4Me$-*o*



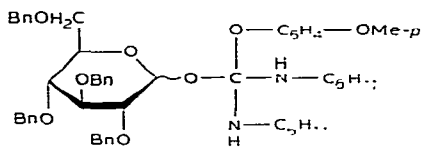
54



55



56



57

(0.01 mol. equiv.), and a phenol (3 mol. equiv.): the results thus obtained are summarized in Table III (Entries 1–17). Except in a few cases, the corresponding 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosides were obtained in 80–90% yield. From these mixtures, the corresponding *β* anomers were isolated in crystalline form in the yields shown in the penultimate column of Table III. According to Vowinkel[13], *O*-methylation of phenols by use of 1,3-dicyclohexyl-*O*-methylpseudourea was induced more rapidly when the phenols had electron-withdrawing than electron-donating substituents, and an *o*-methyl group showed no effect on the ether formation.

However, the ortho effect has been observed in the reaction of *o*-methylphenol, which gave the corresponding D-glucopyranosides in a lower yield than the *m*- and *p*-isomers. The phenols substituted with an *o*-nitro or *o*-formyl group, which can form intramolecular hydrogen-bonds, tend to give the corresponding D-glucopyranosides in yields higher than those in the reactions with the *m*- and *p*-isomers. All of the 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosides were obtained in fairly good yields, regardless of the electronic effect of the substituents on the phenyl groups. Extension of the two-stage procedure to substituted naphthols (**38–41**) and benzenethiols (**46** and **47**), moreover, gave the corresponding D-glucopyranosides (**42–45**, **48**, and **49**) in excellent yields, as shown in Entries 18–23 in Table III.

Reaction using diisopropylcarbodiimide (**3**) *in chloroform solution.* — Carbodiimide **3** was found to be inadequate for the fusion procedure, as **1** was not co-fusible with **3** (3 mol. equiv.) in the presence of copper(I) chloride at 80–85°. In this case,

TABLE III

SYNTHESIS OF ARYL D-GLUCOPYRANOSIDE AND 1-THIO-D-GLUCOPYRANOSIDE DERIVATIVES BY PROCEDURE 3[a]

Entry	Nucleophiles	Yield (%) of D-glucoside[b]			β Anomer M.p. (°C)[c]	β Anomer $[\alpha]_D^{23}$ (degrees) (c 1.0, $CHCl_3$)	β Anomer Formula	β Anomer Elementary analysis[d] C	H	N[S](%)	α Anomer ^1H-n.m.r. data for H-1 δ	$J_{1,2}$ (Hz)	Recovery (%) of 1
1	6	22	93	(77)	94.5–95.5 (M) (*lit.*[e] 78	−4 −2.4)	$C_{41}H_{42}O_7$	76.36 (76.14	6.55 6.55)		5.38	3.5	2
2	7	23	84	(61)	80–81 (C) (*lit.*[e] 76	−12 −9.8)	$C_{40}H_{40}O_6$	78.03 (77.90	6.55 6.54)		5.45	3.7	N.d.[f]
3	8	24	84[g]	(35)	112.5–114 (B) (*lit.*[e] 97–98	−33.5)	$C_{40}H_{39}NO_8$	72.66 (72.60	5.95 5.94	2.22 2.12)	5.45	3.5	N.d.
4	9	25	81	(11)	89.5–90 (C)	−35	$C_{40}H_{39}NO_8$	72.65 (72.60	5.87 5.96	2.00 2.12)	5.45	3.5	5
5	10	26	89	(35)	112–113 (C)	−6	$C_{40}H_{39}NO_8$	72.76 (72.76	5.96 5.94	2.06 2.12)	5.48	3.0	N.d.
6	11	27	91	(64)	87–87.5 (M)	−9	$C_{41}H_{42}O_6$	78.18 (78.07	6.72 6.71)		5.45	3.5	N.d.
7	12	28	90	(62)	76–77 (M)	−13	$C_{41}H_{42}O_6$	78.07 (78.07	6.76 6.71)		5.49	3.5	N.d.
8	13	29	76	(63)	97–99 (M) (*lit.*[e] 94	−12 −8.8)	$C_{41}H_{42}O_6$	77.88 (78.07	6.65 6.71)		5.49	3.5	5
9	14	30	88	(59)	95–96 (M)	−14	$C_{40}H_{39}ClO_6$	73.95 (73.74	5.97 6.03)		5.38	3.2	N.d.
10	15	31	93	(52)	94–94.5 (M) (*lit.*[e] 67	−19 −16.9)	$C_{40}H_{39}ClO_6$	73.62 (73.74	5.89 6.03)		5.38	3.3	N.d.

11	16	32	87	(67)	114.5–116 (M)	−27	$C_{40}H_{39}ClO_6$	73.87 (73.74	5.82 6.03)		5.48	3.5	N.d.
12	17	33	87	(50)	107–108 (M)	−25	$C_{41}H_{39}NO_6$	76.87 (76.73	6.18 6.13	2.13 2.18)	5.43	3.5	5
13	18	34	85	(66)	130.5–132 (M)	−45	$C_{41}H_{39}NO_6$	76.86 (76.73	6.07 6.13	2.22 2.18)	5.47	3.3	N.d.
14	19	35	67	(44)	106–107 (M)	−31	$C_{41}H_{40}O_7$	76.40 (76.37	6.29 6.25)		5.51	3.5	26
15	20	36	74	(54)	132–133 (M)	−33	$C_{41}H_{40}O_7$	76.44 (76.37	6.26 6.25)		5.48	3.0	19
16	21	37	46	(38)	111–112 (M)	−34	$C_{42}H_{42}O_8$	74.82 (74.76	6.33 6.27)		5.56	3.3	46
17	38	41	88	(56)	131–132 (M) (*lit.*[r] 130	−50 −54.9)	$C_{44}H_{42}O_6$	78.93 (79.25	6.53 6.35)		5.63	3.0	N.d.
18	39	43	92	(65)	113–114 (M)	−19	$C_{44}H_{42}O_6$	79.05 (79.25	6.28 6.35)		5.63	3.2	N.d.
19	48	44	84	(31)	100–102 (B,C)	−24	$C_{44}H_{41}NO_8$	74.06 (74.24	5.73 5.81	1.91 1.97)	5.55	3.5	N.d.
20	41	45	82	(60)	143.5–144.5 (B,C)	−29	$C_{54}H_{40}N_2O_{10}$	69.92 (69.83	5.35 5.33	3.70 3.70)	5.65	3.2	N.d.
21	46	48	N.d.	(83)	92.5–93.5 (M) (*lit.*[e] 88	−3 −5.1)	$C_{40}H_{40}O_5S$	75.91 (75.93	6.36 6.37	[5.11] [5.06])	N.d.	N.d.	N.d.
22	47	49	94	(74)	116–117 (M)	−9	$C_{40}H_{39}ClO_5S$	72.24 (72.01	5.93 5.89	[4.86] [4.80])	5.58	4.0	N.d.

[a]All reactions were performed by use of **1** (2.0 mmol), **2** (6.0 mmol), and CuCl (0.02 mmol), with heating for 0.5 h at 80–85°; the nucleophile (6.0 mmol) was then added, and the mixture was heated for 1 h at 80–85°. [b]The yields shown in parentheses are of the β anomers obtained by crystallization of each resulting mixture of D-glucopyranosides. [c]B, C, and M (shown in parentheses) stand for benzene, cyclohexane, and methanol, respectively. [d]Data of elementary analyses shown without parentheses are Found, and those shown in parentheses below the Found data are Calculated. [r]See ref. 12. [f]N.d. = Not determined. [g]$\alpha:\beta$ = 3:17; this ratio was calculated in terms of the area-ratios of the C-1 signals at δ 95.3 (α anomer) and 100.1 (β anomer) in the ^{13}C-n.m.r. spectrum.

TABLE IV

EXAMINATION OF REACTION CONDITIONS FOR THE SYNTHESIS OF **27** IN CHLOROFORM

Entry	*Reagent (mmol)*				*Reaction conditions*		*Yield (%) of*		*Recovery (%) of*
	1	**3**	*CuCl*	**11**	*Temp. (°C) (time)*		**27**	[α:β[a] β[b]]	**1**
					First stage	*Second stage*			
1	2.0	2.2	0.02	2.2	20–25 (2 d)	20–25 (6 d)	77	[12:88 49]	19
2	2.0	2.2	0.02	2.2	20–25 (2 d)	20–25 (30 d)	75	[15:85 55]	0
3	2.0	2.2	0.02	2.2	20–25 (2 d)	reflux (2 d)	75	[24:76 54]	11
4	2.0	2.2	0.02	6.6	20–25 (2 d)	20–25 (2 d)	79	[12:88 52]	4
5	2.0	2.2	0.02	6.6	20–25 (2 d)	reflux (2 d)	82	[19:81 53]	13
6	2.0	6.6	0.02	6.6	20–25 (2 d)	20–25 (2 d)	65	[16:84 44]	17
7	2.0	2.2	0.02	2.2	reflux (0.5 h)	reflux (1 h)	28	[56:44 N.d.[c]]	67
8	2.0	2.2	0.02	2.2	reflux (2 h)	reflux (1 h)	62	[29:71 39]	25

[a]These proportions were calculated in terms of the area-ratios of the methyl-proton signal at δ 2.3 and the H-1 signal of the α anomer at δ 5.45 in the ^{1}H-n.m.r. spectra. [b]These yields were of **27** crystallized from methanol. [c]N.d. = not determined.

therefore, the reaction was performed in a solvent by use of model compounds, *p*-methylphenol (**11**) and **3**, leading to formation of the *p*-methylphenyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosides (**27**). As the solvent for the reaction, *N*,*N*-dimethylformamide and chloroform were examined from the standpoint of their excellence as solvents, but the former was, unexpectedly, inadequate for the pseudourea formation reaction, giving some products chromatographically less polar than **1**. On the other hand, ethanol-free chloroform was effective for the coupling reaction; the results thus obtained are summarized in Table IV.

Treatment of **1** with **3** (1.1 mol. equiv.) in the presence of copper(I) chloride* at 20–25° caused completion of formation of the corresponding pseudourea within 2 days. Prolongation of the reaction time gave additional, less-polar products (judging from t.l.c. of the reaction mixture), although a small proportion of unchanged **1** remained in the mixture. Thus, the resulting mixtures from the reaction of **1** with **3** in the presence of copper(I) chloride in chloroform were respectively treated with **11** under the conditions shown in Entries 1–8 (Table IV).

Among the reactions with 2.2 mmol of **11** in the second stage (Entries 1–3), no difference in the yields of **27** was observed: it was concluded that it is sufficient to perform the reaction for 6 days at room temperature, and that 30 days was inappropriate for isolation of **27**, because of undesirable discoloration. Reaction under reflux in the second stage (Entry 3) made it possible to shorten the reaction time to

*Basic copper(II) carbonate and copper(II) sulfate pentahydrate were ineffective, giving no product even on performing the reaction for a week. Anhydrous copper(II) sulfate gave a small yield of the pseudourea. Copper(II) chloride dihydrate and anhydrous copper(II) chloride respectively gave the pseudourea in ~ 50 and 70% yield.

TABLE V

COMPARISON OF FOUR CARBODIIMIDES (2, 3, 4, AND 5) FOR THE SYNTHESIS OF 27 IN CHLOROFORM[a]

Entry	*Carbodiimide*	*Reaction conditions* Temp. (°C) (time)		*Yield (%) of* 27	[α:β[b] β[c]]	*Recovery (%) of* 1
		First stage	*Second stage*			
1	2	20–25 (2 d)	20–25 (6 d)	78	[21:79 60]	19
2	2	reflux (2 h)	reflux (1 h)	44	[14:86 29]	43
3	3	20–25 (2 d)	20–25 (6 d)	77	[12:88 49]	19
4	3	reflux (2 h)	reflux (1 h)	62	[29:71 39]	25
5	4	20–25 (2 d)	20–25 (6 d)	70	[18:82 48]	26
6	4	reflux (2 h)	reflux (1 h)	55	[22:78 32]	41
7	5	20–25 (2 d)	20–25 (6 d)	32	[16:84 23]	61
8	5	reflux (2 h)	reflux (1 h)	26	[21:79 15]	70

[a]After the formation of the *O*-D-glucopyranosylpseudourea derivatives (**50**, **51**, **52**, and **53**, respectively) from **1** (2.0 mmol), carbodiimides **2**, **3**, **4** and **5** (2.2 mmol), and CuCl (0.02 mmol) in chloroform (2 mL), compound **11** (2.2 mmol) was added. [b]The ratios were calculated in terms of the area-ratios of the methyl-proton signals at δ 2.3 and the H-1 signal of the α anomer at δ 5.45 in the ^{1}H-n.m.r. spectra. [c]Yields of **27** isolated by crystallization from methanol.

1 h. Use of 6.6 mmol of **11** (Entries 4 and 5), and that of **3** and **11** (Entry 6) to **1** (2.2 mmol) did not cause much improvement in the yield of **27**.

The ratios of the α and β anomers (determined by ^{1}H-n.m.r. spectroscopy) formed in these reactions were, by and large, centered around 3:17, except for Entry 3. Moreover, attempts at shortening the reaction time of the first stage of the reaction by refluxing the chloroform solution (Entries 7 and 8) were rather unfruitful, giving **27** in lower yields, and the ratios of the anomers deviated from those shown in Entries 1–6. Judging from the improvement in the ratio from 14:11 to 29:71, the result in Entry 7 may imply incompleteness of formation of the pseudourea **7**, and that in Entry 8 may be exceptional, leading to a better yield of **27**, in addition to improvement in the ratio of the anomers. These results indicate that the two-stage procedure, involving, as the first stage, the reaction of **1** with 1.1 mol. equiv. of **3** in chloroform for 2 days at 20–25°, and as the second, treatment of the resulting mixture with a phenol for 6 days at 20–25° or under reflux for 1 h, is superior to the fusion procedure described.

Finally, the possible effect of substituents on the nitrogen atoms of the carbodiimides was examined by use of di-*p*-tolyl- (**4**) and di-*o*-tolyl-carbodiimide (**5**), instead of **2** and **3**, with respect to synthesis of **27** catalyzed by copper(I) chloride; the results thus obtained are summarized in Table V, together with the conditions used. Except in the case of the reaction through **5**, there was no significant difference among the reactions, judging from the good yields of **27**. T.l.c. of the mixture resulting from the first-stage reaction using **5** proved that the yield of the corresponding pseudourea derivative (**53**) was poorer than those of the other pseudoureas (**50**, **51**,

and **52**), and that a considerable amount of **1** remained unchanged; this may reflect the ortho effect, by the *o*-methyl substituent, on pseudourea formation. On the other hand, the reaction under reflux in both stages (Entries 2, 4, 6, and 8) was inferior to each of the foregoing at room temperature. The first stage of each synthesis is crucial for formation of the pseudourea; however, the reaction time could not be further prolonged as t.l.c. proved that the first-stage reaction gave products less polar than the corresponding pseudourea derivatives and, in addition, that the yields of the pseudourea derivatives varied, probably due to steric and electronic effects of the substituents on the nitrogen atoms of the carbodiimides. Consequently, **3** and **4** proved useful for the formation of D-glucopyranosides. The reactions were assumed to proceed by way of the corresponding *O*-D-glucopyranosylpseudourea derivatives, as the $\alpha:\beta$ ratios of the anomers produced ranged from 1:4 to 3:7.

Reaction mechanism. — In order to make it possible to discuss the steric aspects of the reactions, we attempted to isolate the *O*-glycosylpseudourea intermediates in pure, crystalline form after the preparation of each pseudourea derivative. Attempts at their purification on a column of silica gel or on one pre-treated with alkali, were all unsuccessful, compound **1** being recovered almost quantitatively.

According to Schmidt and Moosmüller[7], it is possible to isolate pseudourea derivatives as their complexes with oxalic acid. Attempts at isolation of the complex of the *O*-glycosylpseudoureas were, however, unsuccessful, compound **1** being recovered quantitatively. These results indicate that the *O*-glycosylpseudoureas, *i.e.*, the pseudoureas of hemiacetal (lactol) hydroxyl groups, are much more labile than those of ordinary alcohols, being hydrolyzed very readily, even on silica gel; this is in accordance with the behavior reported by Vowinkel[13], *i.e.*, 1,3-dicyclohexyl-*O*-methylpseudourea gave *p*-methoxyphenyl methyl ether in 57% (30 min), and 93% yield (14 h) on reaction* at 100° with *p*-methoxyphenol. Therefore, attempts to isolate the *O*-D-glucopyranosylpseudourea derivatives were abandoned, and the syrupy product resulting from the reaction of **1** with **2** in the presence of copper(I) chloride, followed by removal of the catalyst by washing with M aqueous ammoniacal solution, drying over anhydrous sodium sulfate**, and evaporation, was examined by i.r. and ^{13}C-n.m.r. spectroscopy. The syrup gave a strong absorption band at 1670 cm^{-1}, specific for a C=N bond. On the other hand, it gave ^{13}C-n.m.r. signals, at δ 89.9, 95.0, 95.6, and 99.8 in the anomeric-carbon region, due to anomeric and geometrical isomerism with respect to the C=N bond of the pseudourea derivative (**50**). It was impossible to assign all four of the signals, but that at δ 89.9, which appeared as the most-intense peak, was assumed to arise from one of the α anomers, on the basis of the results reported by Haverkamp *et al.*[15] (see Fig. 1). Therefore, the resulting pseudourea mixture was proved to contain the corresponding α anomers

*O-D-Glucopyranosylpseudoureas from **1** are reactive enough in the reaction with acetic acid to give[8] the 1-*O*-acetyl derivatives in 88% yield within 2 h at 0°; this is in contrast with the reaction of 1,3-dicyclohexyl-*O*-methylpseudourea, with requires 1.5 h at 60° for its completion[11].

The use of anhydrous magnesium sulfate (instead of sodium sulfate) unexpectedly gave 1,3-dicyclohexyl-1-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)urea (54**) in 48% yield.

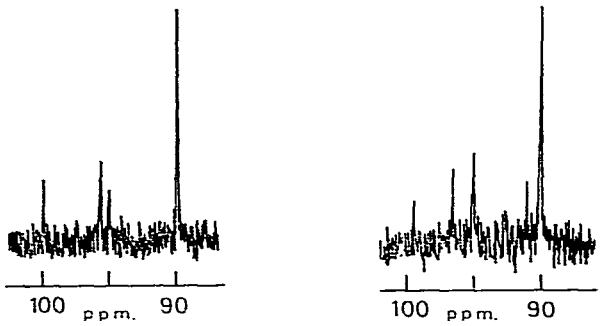
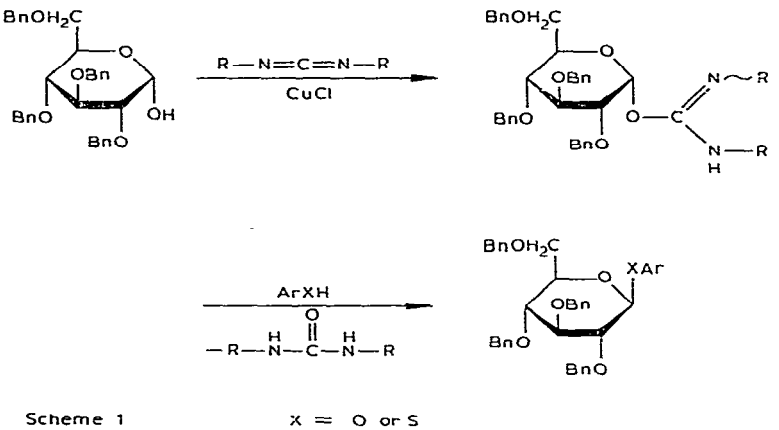


Fig. 1. Anomeric region in the ^{13}C-n.m.r. spectrum ($CDCl_3$–Me_4Si) of pseudourea **50**.

Fig. 2. Anomeric region in the ^{13}C-n.m.r. spectrum ($CDCl_3$–Me_4Si) of pseudourea **51**.



Scheme 1 X = O or S

TABLE VI

REACTIONS OF **1** WITH **55** AND THOSE CATALYZED BY CuCl[a]

Entry	*Solvent*	*Catalyst*	*Conditions* *Temp.* (°C) (*time*)	*Yield (%) and α:β ratio* **22**	[α:β][b]	**56**	[α:β][c]	*Recovery (%) of* **1**
1	chloroform	—	20–25 (30 d)	28	[21:79]	3	[—]	~60
2	chloroform	CuCl	20–25 (30 d)	9	[—]	13	[49:51]	~70
3	—	—	100–105 (3 h)	20	[23:77]	12	[41:59]	~50
4	—	CuCl	100–105 (3 h)	15	[38:62]	33	[43:57]	~35

[a]In all reactions, **1** (1.0 mmol), **55** (1.0 mmol), and CuCl (catalytic amount, when used) were employed. [b]These ratios were calculated in terms of the area-ratios of the C-1 signals at δ 96.5 (α anomer) and 102.8 (β anomer) in the ^{13}C-n.m.r. spectra. [c]These ratios were calculated in terms of the area-ratios of the H-1 signals at δ 6.13 (α anomer) and 5.58 (β anomer) in the ^1H-n.m.r. spectra.

preponderantly, judging from the ratios of the areas of the four signals. Similarly, the syrupy pseudourea derivative mixture, **51**, prepared by the reaction of **1** with **3** in chloroform, was examined; it give a specific, i.r. absorption band at 1670 cm^{-1}, and anomeric ^{13}C-n.m.r. signals at δ 89.7, 95.7, 98.7, and 99.9, the first of which was the most intense and was assigned to the α anomer (see Fig. 2); it was thus proved to contain mainly the corresponding α anomer. Therefore, it was concluded that the nucleophilic-substitution reaction in the second stage proceeds *via* an SN2-like mechanism, to give mainly the corresponding β-D-glucopyranoside, as depicted in Scheme 1.

The reactions performed by Procedure 1 and 2 (one-stage reaction) were found to bring about low regioselectivity in the formation of **22**. This may indicate the possibility that formation of the D-glucopyranosides proceeds *via* 1,3-dicyclohexyl-*O*-(*p*-methoxyphenyl)pseudourea (**55**). Therefore, we examined some reactions of **1** with **55**: the conditions used and the results thus obtained are summarized in Table VI. In all of the cases shown in Entries 1–4, the yields of **22** were low, despite very long reaction-times, and **22** was obtained together with 2,3,4,6-tetra-*O*-benzyl-1-*O*-(cyclohexylcarbamoyl)-D-glucopyranose (**56**). Moreover, a reasonable amount of **1** was recovered in each reaction, and the fusion reactions (Entries 3 and 4) were performed at 100–105°, because **1** and **55** cannot be co-fused at ~80°. Furthermore, the yield of **56** was found to increase in the reactions catalyzed by copper(I) chloride (see Entries 1 and 2, and 3 and 4). The formation of the by-product **56**, and the ratios of the anomers of **22** [*cf.* Tables I (procedures 1 and 2) and VI], led us to conclude that the one-stage reaction does not involve both **55** and **57** as reaction intermediates (the latter should be formed by the addition of **1** to **55**). Such an acetal type of intermediate as **57** had been postulated in synthetic studies on methoxybenzenes[6]. On the other hand, it is at present impossible to discuss the formation of **56** (see Table VI) mechanistically.

In the one-stage reaction, carbodiimides may be activated by phenols, as has been proposed for explaining the mechanism of formation of methoxybenzenes[6] in the absence of the catalyst, and in the presence of copper(I) chloride, involving the addition of **1** to give the pseudourea **50**, which then undergoes reaction with the phenol. Moreover, the ratio of the anomers in **22** ($\alpha:\beta$ = ~3:2) might be due to anomerization of **1** catalyzed by a phenol or phenoxide ion, giving **50** with an anomeric ratio such as to give the ratio in **22**.

It is thus concluded that carbodiimides are effective reagents for the coupling of phenols with sugar derivatives having the anomeric hydroxyl group free.

EXPERIMENTAL

General. — Melting points were determined with a Yanagimoto Micro Melting Point Apparatus and are uncorrected. Optical rotations were measured with a Hitachi PO-B polarimeter. T.l.c. was performed on precoated plates (thickness 0.20 mm) of silica gel 60 (Merck F_{254}) with 9:1 (v/v) benzene–acetone, and detection of spots

was effected with sulfuric acid. Column chromatography was performed on Wakogel C-300 (Wako Pure Chemical Industries, Ltd.). Solvent proportions used for elution are given in volume per volume (v/v). Elemental analyses were made with a Perkin–Elmer 240-0002 instrument. Dicyclohexylcarbodiimide (**2**) was purchased from Wako Pure Chemical Industries, Ltd., diisopropylcarbodiimide (**3**) from Nakarai Chemicals, and di-*p*- (**4**) and di-*o*-tolyl-carbodiimide (**5**) from Aldrich Co. N.m.r. spectra (^1H and ^{13}C) were respectively recorded with a Varian T-60 and a CFT-20 instrument, for solutions in chloroform-*d*, with tetramethylsilane as the internal standard. I.r. spectra were recorded with a Hitachi 285 spectrometer.

*2,3,4,6-Tetra-*O*-benzyl-α-*D*-glucopyranose* (**1**). — Compound **1** was prepared from D-glucose according to the method reported by Glaudemans and Fletcher[10]; m.p. 151–152° (from methanol) [lit.[10] 151–152° (from methanol)], R_F 0.50.

Comparative examination of Procedures 1, 2, and 3 for the synthesis of **22**. — *Procedure 1.* A mixture of **1** (1.080 g, 2.0 mmol), **2** (415 mg, 2.0 mmol), and *p*-methoxyphenol (**6**) (248 mg, 2.0 mmol) was fused for 3 h at 80–85°. The resulting mixture was chromatographed on a column of silica gel (25 g); use of 1 : 1 benzene–cyclohexane containing 1% of acetone for elution gave *p*-methoxyphenyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**22**) (207 mg, 16% yield), and use of that containing 4% of acetone gave **1** (789 mg, 73% recovery).

Procedure 2. A mixture composed of the foregoing mixture and copper(I) chloride (2 mg, 0.02 mmol) was fused for 15 h at 80–85°, and the resulting mixture was treated as described in Procedure 1.

Procedure 3 (two-stage reaction). A mixture of **1** (1.080 g, 2.0 mmol), **2** (415 mg, 2.0 mmol), and copper(I) chloride (2 mg, 0.02 mmol) was fused for 0.5 h at 80–85°, and then fusion was continued for 1 h at the same temperature after the addition of **6** (248 mg, 2.0 mmol). The resulting mixture was treated as already described. The ratio of the anomers in **22** was calculated in terms of area-ratios of C-1 signals; the α and β anomer gave their signals at δ 96.5 and 102.8, respectively. Compound **50** had R_F 0.0–0.2. All of the results thus obtained are summarized in Table I, together with the conditions used.

Examination of reaction conditions in fusion reaction of **1** *with* **6** *by Procedure 3.* — A series of reactions was performed by use of the reagents **1**, **2**, copper(I) chloride, and **6** with the molar proportions summarized in Entries 1–8 in Table II. A solution of the resulting mixture in chloroform (30 mL) was mixed with M oxalic acid solution in acetone (5 mL) and stirred for 1 h at room temperature; during this treatment, unchanged **2** was converted into 1,3-dicyclohexylurea[16]; this was removed by filtration, and the filtrate was successively washed with M aqueous sodium hydroxide solution (10 mL) and water (10 mL), dried (anhydrous sodium sulfate), and evaporated to a syrup which was chromatographed on a column of silica gel (25 g) as already described. In Entry 5, for example, **22** (1.201 g, 93% yield) having an anomeric ratio of α:β = 17:83 was obtained; this gave the β anomer (995 mg, 77% yield) on crystallization from methanol.

Copper(I) chloride was removed after the first stage by successively washing

the chloroform solution with M aqueous ammoniacal solution (20 mL) and water (20 mL), drying (anhydrous sodium sulfate), and evaporating to a syrup, for use for the next coupling reaction with **6** (as shown in Entry 6). All of the results are given in the last column of Table II.

Synthesis of aryl D-*glucopyranoside and 1-thioglucopyranoside derivatives by Procedure 3.* — After the manner of Procedure 3, a mixture of **1** (1.080 g, 2.0 mmol), **2** (1.245 g, 6.0 mmol), and copper(I) chloride (2 mg, 0.02 mmol) was first fused for 30 min at 80–85°, and to each such resulting mixture was respectively added 6.0 mmol of **6–21**, **38–41**, **46**, or **47**, and the fusion was continued for 1 h at the same temperature. All of the resulting mixtures were treated as already described; the results are summarized in Table III, together with the properties, the results of elementary analyses of the β anomer of **22–37**, **42–45**, **48**, and **49**, respectively, and the ^{1}H-n.m.r. data for each of the corresponding α anomers.

Examination of reaction conditions for the synthesis of **27** *in chloroform solution by use of diisopropylcarbodiimide* (**3**). — Compound **1** (1.080 g, 2.0 mmol), **3** (280 mg, 2.2 mmol), and copper(I) chloride (2 mg, 0.2 mmol) were dissolved in ethanol-free chloroform, and the resulting solution was stirred for 2 days at 20–25°; *p*-methylphenol (**11**; 232 mg, 2.2 mmol) was then added, to couple with the resulting pseudourea derivative at 20–25° or under reflux. The resulting mixture was evaporated to a syrup, whose ^{1}H-n.m.r. spectrum made possible the calculation of the ratios of the anomers in terms of the area-ratio of the C-methyl proton signal at δ 2.3, and the H-1 signal of the α anomer at δ 5.45. Crystallization of the syrup from methanol gave the corresponding β anomer. All of the results thus obtained are summarized in Table IV, together with the conditions used. The *O*-D-glucopyranosyl-1,3-diisopropylpseudourea (**51**) had R_F 0.0–0.2.

Comparative examination of four carbodiimides (**2**, **3**, **4**, *and* **5**) *for the synthesis of* **27** *in chloroform.* — All of the reactions were performed by use of the four carbodiimides, *i.e.*, **2**, **3**, **4**, and **5**, as for the foregoing reactions in chloroform. The results thus obtained are summarized in Table V, together with the conditions used. The *O*-D-glucopyranosylpseudourea derivatives, both **52** and **53**, had an R_F value of 0.65.

Rearrangement of **50** *into* **54**. — After fusion of **1** (1.080 g, 2.0 mmol), **2** (1.240 g, 6.0 mmol), and copper(I) chloride (2 mg, 0.02 mmol) for 30 min at 80–85°, the mixture was dissolved in chloroform (20 mL), and the solution was successively washed with M aqueous ammoniacal solution (20 mL) and water (20 mL), dried (anhydrous magnesium sulfate; ~10 g) overnight, and evaporated, and the resulting syrup was chromatographed on a column of silica gel (25 g). Elution with 1 : 1 benzene–cyclohexane containing 3% of acetone gave **54** (687 mg, 46% yield) and, subsequently, **1** (533 mg, 50% recovery).

Compound **54** was a syrup, $[\alpha]_D^{23}$ +60° (*c* 0.6, chloroform); R_F 0.6; ν_{max}^{NaCl} 1650 (C=O) and 3370 cm^{-1} (N-H): ^{1}H-n.m.r. data: δ 5.49 (d, 1 H, $J_{1,2}$ 7.0 Hz, H-1).

Anal. Calc. for $C_{47}H_{58}N_2O_6$: C, 75.57; H, 7.83; N, 3.75. Found: C, 75.45; H, 7.85; N, 3.66.

1,3-Dicyclohexyl-O-(p-*methoxyphenyl*)*pseudourea* (**55**). — According to the

method reported by Vowinkel and Wolff[17], compound **55** was prepared from **2** and **6**; m.p. 90–91° (from benzene–hexane) [lit.[17] m.p. 90–91° (from benzene–hexane)].

The reaction of **55** *with* **1**: *formation of* **56**. — A mixture of **1** (540 mg, 1.0 mmol) and **55** (330 mg, 1.0 mmol) was treated in chloroform, or by fusion, under the conditions shown in the first part of Table VI. The reactions in chloroform were followed by evaporation. The resulting syrup was chromatographed on a column of silica gel (25 g). Elution with 1:1 benzene–cyclohexane containing 1% of acetone afforded **22**. On increasing the content of acetone to 3%, 2,3,4,6-tetra-*O*-benzyl-1-*O*-(cyclohexylcarbamoyl)-D-glucopyranose (**56**), at first the α anomer and then the β anomer, and **1**, together with small amounts of 1,3-dicyclohexylurea and **55** were isolated. The results are summarized in Table VI.

The α anomer of **56** had m.p. 102–104° (from methanol): $[\alpha]_D^{23}$ +58° (*c* 1.0, chloroform); R_F 0.63; ν_{max}^{KBr} 1700 cm^{-1} (C=O); ^{1}H-n.m.r. data: δ 6.13 (d, 1 H, $J_{1,2}$ 2.9 Hz, H-1).

Anal. Calc. for $C_{41}H_{47}NO_7$: C, 73.96; H, 7.12; N, 2.10. Found: C, 74.15; H, 7.21; N, 1.91.

The β anomer of **56** had m.p. 146–148° (from methanol): $[\alpha]_D^{23}$ +10° (*c* 1.0, chloroform); R_F 0.61; ν_{max}^{KBr} 1700 cm^{-1} (C=O); ^{1}H-n.m.r. data; δ 5.58 (d, 1 H, $J_{1,2}$ 7.0 Hz, H-1).

Anal. Calc. for $C_{41}H_{47}NO_7$: C, 73.96; H, 7.12; N, 2.10. Found: C, 73.95; H, 7.14; N, 1.90.

ACKNOWLEDGMENT

The authors thank Miss Mikiko Aoki, Laboratory of Organic Analysis, Department of Chemistry, Tokyo Institute of Technology, for the microanalyses.

REFERENCES

1 Y. Ishido, N. Sakairi, K. Okazaki, and N. Nakazaki, *J. Chem. Soc., Perkin Trans. 1*, (1980) 563–573.
2 H. G. Khorana, *Chem. Rev.*, 53 (1953) 145–166.
3 F. Kruzer and K. Douaghi-Zadeh, *Chem. Rev.*, 67 (1967) 107–152.
4 L. J. Mathias, *Synthesis*, (1979) 561–576.
5 F. L. Bach, *J. Org. Chem.*, 30 (1965) 1300–1301.
6 E. Vowinkel, *Chem. Ber.*, 99 (1966) 42–47.
7 E. Schmidt and F. Moosmüller, *Justus Liebigs Ann. Chem.*, 597 (1955) 235–240.
8 H. Tsutsumi, Y. Kawai, and Y. Ishido, *Chem. Lett.*, (1978) 629–632.
9 (a) G. Wolff and G. Röhle, *Angew. Chem., Int. Ed. Engl.*, 13 (1974) 157–170; (b) K. Igarashi, *Adv. Carbohydr. Chem. Biochem.*, 34 (1977) 243–283.
10 C. P. J. Glaudemans and H. G. Fletcher, Jr., *Methods Carbohydr. Chem.*, 6 (1972) 373–376.
11 E. Däbritz, *Angew. Chem.*, 78 (1966) 483–490.
12 K. Brewster, J. M. Harrison, and T. D. Inch, *Tetrahedron Lett.*, (1979) 5051–5054.
13 E. Vowinkel, *Chem. Ber.*, 99 (1966) 1479–1484.
14 E. Vowinkel, *Chem. Ber.*, 100 (1967) 16–22.
15 J. Haverkamp, M. J. A. Bie, and J. F. G. Vliegenthart, *Carbohydr. Res.*, 37 (1974) 111–125.
16 F. Zetzsche and A. Fredrich, *Ber.*, 72 (1939) 363–365.
17 E. Vowinkel and C. Wolff, *Chem. Ber.*, 107 (1974) 907–914.