ZINC *p*-*tert*-BUTYLBENZOATE CATALYZED GLYCOSYLATION WITH GLYCOPYRANOSYL CHLORIDE

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A 0.1 eq of zinc *p*-*tert*-butylbenzoate significantly accelerates glycosylation of alcohol with glycopyranosyl chloride in the presence of 2-methyl-2-butene to give β -glycoside in high yield with fair to good β -selectivity.

KEYWORDS zinc *p*-*tert*-butylbenzoate; catalytic; glycosylation; glucopyranosyl chloride; β -glucoside

Although a large number of glycosylation procedures have been developed, leaving groups at anomeric centers are usually activated by a stoichiometric amount of reagent.¹⁾ Recently we have reported Zn(acac)₂ catalyzed rhamnosylation of cholesterol with 2,3,4-tri-*O*-benzyl- α -L-rhamnopyranosyl chloride that affords α -rhamnoside selectively.²⁾ When this procedure was applied to glucosylation, the yield and stereoselectivity were not satisfactory. Thus we have tried to find a more efficient catalytic system for the glucosylation with D-glucopyranosyl chlorides. After examination of most of the commercially available zinc salts, we arrived at zinc *p*-*tert*-butylbenzoate as a catalyst. A variety of glucosides were prepared in generally high yield with fair to good β -selectivity within a few hours at room temperature in dichloromethane by using 0.1 eq of the catalyst. In particular the 2' hydroxyl group of nonprotected glucosyl chloride afforded a higher β -selectivity.

Reactions of cholesterol (**3**) with 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranosyl chloride (**1**) were carried out in the presence of a variety of zinc salt as catalyst. The results are summarized in Table I. Although 2-methyl-2-butene was employed as an acid scavenger, we found that it also accelerates the reaction significantly (entries 1 and 2) with better stereoselectivity. Except for Zn(OTf)₂, which gave low stereoselectivity (entries 6 and 7),³⁾ most zinc salts provided essentially similar yield and selectivity. Zinc *p*-*tert*-butylbenzoate (**4**) afforded better yield in a β -selective manner (entries 12 and 13). For example, to a dried solution of cholesterol (**3**) (50 mg, 0.13 mmol), zinc *p*-*tert*-butylbenzoate (**4**) (5.4 mg, 0.013 mmol, 0.1 eq), and 2-methyl-2-butene (200 mg, 2.8 mmol, 22 eq) in dichloromethane (8 mL)²⁾ was added a solution of **1** (108 mg, 0.19 mmol) in dichloromethane (7 mL), and the mixture was stirred at room temperature for 3 h. The mixture was directly subjected to a column chromatography on silica gel to give α and β glucosides in 98% yield. Stereoselectivity (α/β ratio) was analyzed by HPLC as well as ¹H NMR to be 13:87.

Condensations of alcohol **9** - **12** with glycosyl chlorides **1**, **2**, **7**, and **8** were carried out in the analogous way, and the results are summarized in Table II. Although the reactions of glucosyl chloride **1** with alcohol **9**-**12** were not stereoselective (entries 2, 3, 4,

and 5), glucosylation with 2' hydroxyl group nonprotected glucosyl chloride **2** afforded a higher β -selectivity by the reaction with cholesterol (**3**) or methyl glucoside **9** (entries 6 and 7). Reaction of amino acid derivatives **10** or **11** with **1** or **2** showed low selectivity (entries 3, 4, 8, and 9). The reaction of **1** and **12** provided four diastereomeric glucosides, and no kinetic resolution was observed (entry 5). Syntheses of galactosides were also achieved by the reaction of galactosyl chloride **7** and alcohols **3** and **9** (entries 10 and 11), and the results were similar to those with the glucosyl chloride **1**. However the reaction of **7** with amino acid derivatives showed α selectivity (entries 12 and 13). Rhamnosylation of cholesterol with **8** afforded quantitative yield but lower selectivity in comparison with Zn(acac)₂-catalyzed reaction.²⁾ It is important to note that the stereochemistry of the methoxyl group of **9** is maintained throughout the zinc salt-catalyzed glycosylation (entries 2, 7, and 11).⁴⁾

Table I. Zn Salt (0.1 eq) Catalyzed Glucosylation of Cholesterol (**3**) with Glucosyl Chloride **1** in the Presence of 2-Methyl-2-butene (22 eq) in Dichloromethane at Room Temperature

Entry	Zn salt	Reaction period (h)	Yield (%)	α/β ratio
1	Zn(acac) ₂	1	57	16:84
2	Zn(acac) ₂	12 ^a	58	23:77
3	ZnCl ₂	1	59	17:83
4	ZnBr ₂	1	76	17:83
5	ZnI ₂	1	76	17:83
6	Zn(OTf) ₂	1	69	43:57
7	Zn(OTf) ₂	0.5 ^b	94	45:55
8	Zn(OCOC ₆ H ₅) ₂	1	60	17:83
9	Zn(OCOC ₆ H ₄ OH- <i>o</i>) ₂	1	64	18:82
10	Zn(OCOCCH ₂ CH ₂ - <i>c</i> -C ₆ H ₁₁) ₂	1	72	17:83
11	Zn(OCOCCH ₂ CH ₂ - <i>c</i> -C ₆ H ₁₁) ₂	2.5	91	15:85
12	Zn(OCOC ₆ H ₄ - <i>t</i> -C ₄ H ₉ - <i>p</i>) ₂ (4)	1	77	17:83
13	Zn(OCOC ₆ H ₄ - <i>t</i> -C ₄ H ₉ - <i>p</i>) ₂ (4)	3	98	13:87

a) Without using 2-methyl-2-butene. b) Reflux temperature in dichloromethane.

Table II. Zn(OCOC₆H₄-*t*-C₄H₉-*p*)₂ (**4**) (0.1 eq) Catalyzed Glycosylation of Alcohol in the Presence of 2-Methyl-2-butene (22 eq) in Dichloromethane at Room Temperature.

Entry	Glycosyl chloride	Alcohol	Reaction period (h)	Yield (%)	α/β ratio
1	1	3	3	98	13:87
2	1	9	2.5	84	30:70
3	1	10	3	90	47:53
4	1	11	3	81	37:63
5	1	12	1	90	26:74
6	2	3	1	97	9:91
7	2	9	2.5	79	2:98
8	2	10	3	52	33:67
9	2	11	1.5	40	50:50
10	7	3	1	98	16:84
11	7	9	1	68	22:78
12	7	10	1	85	65:35
13	7	11	1.25	95	71:29
14	8	3	1	100	64:36

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