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A new and facile synthesis of carbamate- and urea-linked glycoconjugate using modified Curtius rearrangement

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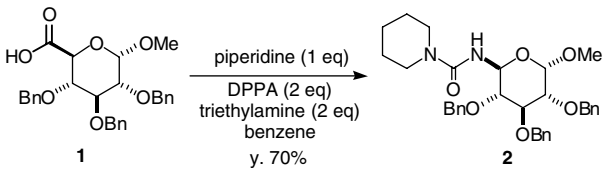
Abstract—We describe a facile synthetic method of carbamate- and urea-linked glycoconjugates using sugar carboxylic acids by the modified Curtius rearrangement. This reaction is a simple one-pot procedure, and various nucleophiles including tertiary alcohols can be utilized to afford desired compounds in moderate to high yields. And the stereospecific synthesis of the anomeric isomers is achieved using the corresponding two stereoisomers of glycosyl carboxylic acid.

There is a large number of glycosides in nature, namely, glycoconjugates such as glycopeptides, glycolipids, and nucleic acids. It is well known that the saccharide moiety of the glycoconjugates plays important roles for their biological activity.[1] Also, there are other glycoconjugate systems whose glycosidic linkage is linked with a carbamate or a urea instead of an acetal linkage.[2] These chemically more stable glycoconjugates[3] are called neoglycoconjugates,[2m] and much attention has been paid to their interesting biological activities. Recently, Ichikawa and Prosperi reported the synthesis of such neoglycoconjugates,[2k–o] and these excellent works overcome the most important problem in the oligosaccharide synthesis, involving the stereoselective synthesis of the anomeric isomers. Their methods are based on an addition of a nucleophile to a sugar isocyanate, and the stereoselective synthesis is achieved by the separation of the anomeric isomers of the sugar isocyanide. We focused on Curtius rearrangement, for one-pot synthesis of carbamate- or urea-linked glycoconjugates by the reaction of sugar carboxylic acid and alcohol or amine using diphenyl phosphoryl azide (DPPA).[4] Curtius rearrangement is known to proceed with retention of the stereochemistry at the carbon connected with the carboxylic acid moiety, and the stereospecific synthesis of anomeric isomers should be accomplished by using the corresponding two stereoisomers of the glycosyl carboxylic acid. Moreover, chemical transformation of carboxylic acids is simple, and that is advantageous for the elongation of oligosaccharides. Here we report a new and facile synthetic method of the neoglycoconjugate using the modified Curtius rearrangement.

We started the Curtius rearrangement reaction using the known D-glucuronic acid derivative (**1**).[5] The general conditions of Curtius rearrangement using DPPA are to react a carboxylic acid and a nucleophile in the presence of triethylamine,[4] and synthesis of a urea-linked saccharide is easily accomplished owing to sufficient nucleophilicity of an amine as shown in Scheme 1.

Compound **1** was refluxed with diphenylphosphoryl azide (DPPA, 2 equiv) and triethylamine (2 equiv) for 1 h and then 1 equiv of piperidine was added to the reaction mixture. Soon the reaction was completed to afford the desired urea-linked saccharide (**2**) in 70% yield. Next, for synthesis of a carbamate-linked saccharide, compound **1** was similarly refluxed with DPPA (2 equiv), triethylamine (2 equiv) and cyclohexanol (1 equiv) as a nucleophile in benzene for 4 h. Unfortunately, the reactivity decreased and the yield was not satisfactory on account of the steric hindrance of the



1 2

Scheme 1.

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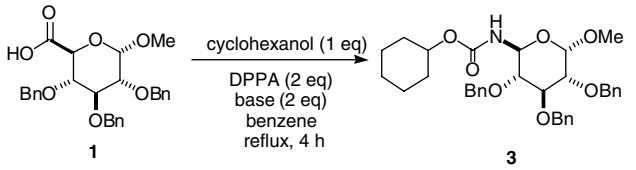
nucleophile. Thus, we investigated at first the basic conditions to activate the nucleophile (Table 1).

Table 1. Base conditions in Curtius rearrangement

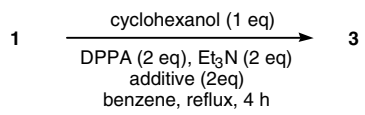


Run	Base	Yield (%)
1	Et_3N	53[a]
2	iPr_2EtN	30
3	DBU	56
4	Li_2CO_3	5
5	Na_2CO_3	52
6	K_2CO_3	69
7	Cs_2CO_3	40
8	K_3PO_4	59

[a] 63% yield after 8 h reflux.

Organic bases resulted in moderate yields of the desired carbamate, although the reactions did not complete and several by-products were obtained by using DBU (runs 1–3). Then, we tried the inorganic bases in spite of their poor solubility in benzene. Gratifyingly, the reaction proceeded smoothly and the best result was obtained by using K_2CO_3 (run 6). However, the isocyanate, intermediate derived from the carboxylic acid in situ, seems to remain as an unreacted form in the reaction mixture with the TLC analysis. And the rate-determining step of this reaction is considered to be an addition of the nucleophile to this reactive isocyanate. Accordingly, we investigated an additional promoter to activate the isocyanate (Table 2). Various additives (2 equiv) were tried with **1**, cyclohexanol, DPPA, and triethylamine in benzene, and in the case of Ag_2CO_3, the reactivity was greatly improved (runs 2–4). The catalytic amounts of Ag_2CO_3 gave the best yield, and a similar effect was also observed with K_2CO_3 as a base. Using $CoCl_2$, the yield was only 5% (run 8); however, it was improved to 47% by adding $CoCl_2$ after confirming the disappearance of carboxylic acid by TLC (run 9). And, a catalytic amount of the additives also brought better results than 2 equiv of them (runs 2, 3 and 11, 12). Therefore, it is suggested that the metal reagents might have some influence on the rearrangement of the carboxylic acid to the isocyanate.

Table 2. Additive conditions in Curtius rearrangement

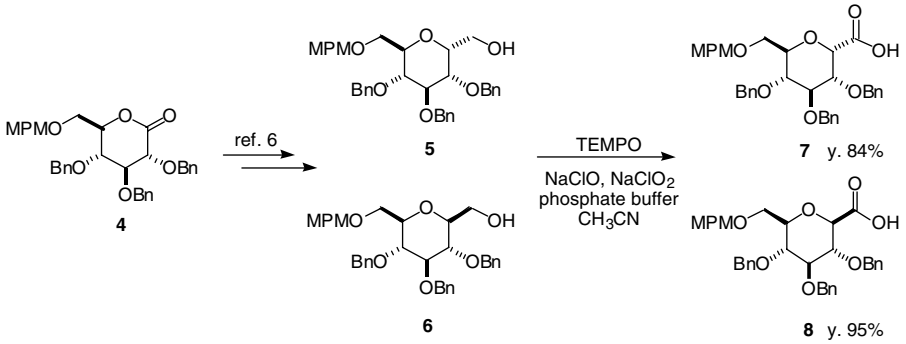


Run	Additive	Yield (%)
1	$BF_3{\cdot}OEt_2$	42
2	Ag_2CO_3	88
3	Ag_2CO_3	95[a]
4	Ag_2CO_3	74[b]
5	Ag_2O	61
6	CuO	68
7	$CuCl_2$	5
8	$CoCl_2$	5
9	$CoCl_2$	47[c]
10	$NiCl_2$	5
11	$ZrCl_4$	47
12	$ZrCl_4$	66[a]
13	$PdCl_2$	15
14	$La(OTf)_3$	20

[a] Additive: 0.1 equiv.
[b] Base: K_2CO_3.
[c] Additive was added after carboxylic acid was disappeared in TLC analysis.

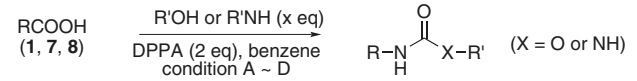
Then, for the synthesis of various glycoconjugate, we prepared both stereoisomers of glycosyl carboxylic acids (Scheme 2). According to the reference,[6] the sugar lactone **4**[7] was transformed into alcohols **5** and **6**, which were then oxidized to the desired carboxylic acids **7** and **8**, respectively. Using compounds **1**, **7**, and **8**, we investigated the reactions with a series of nucleophiles under the above modified Curtius rearrangement conditions (Table 3).

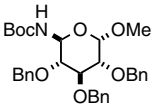
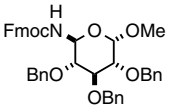
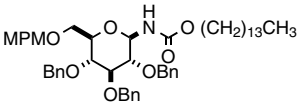
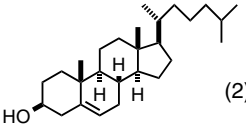
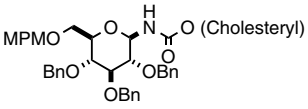
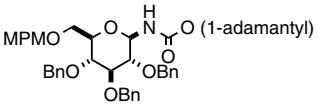
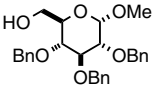
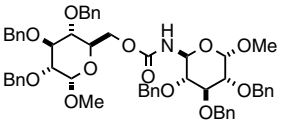
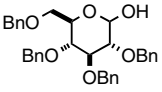
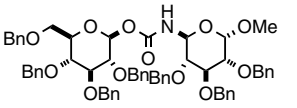
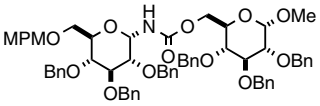
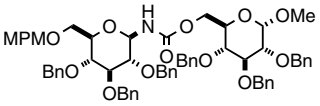
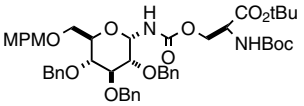
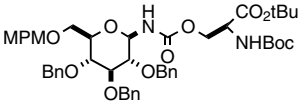
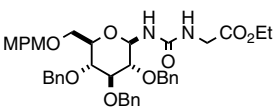
At first, *t*-BuOH was used as a nucleophile. Because of its steric hindrance, an excess amount of *t*-BuOH was necessary to obtain the desired compound (run 1). However, Ag_2CO_3 showed a great effect, and the Boc-protected sugar **12** was obtained in 67% yield with only 3 equiv of *t*-BuOH (run 3). Using K_2CO_3 as a base caused the formation of *t*-BuOK in situ and that resulted in some by-products and low yield (run 4). Second, we attempted to obtain a Fmoc-protected sugar using 9-fluorenemethanol (9-Fm) as a nucloephile. For synthesis of a base-labile Fmoc carbamate using Curtius rearrangement, 9-Fm is generally reacted with an isolated isocyanate after excluding a base that remained



Scheme 2.

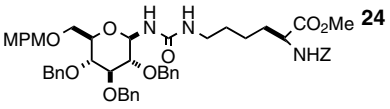
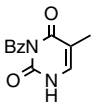
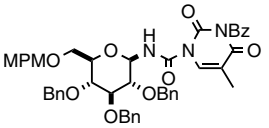
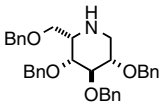
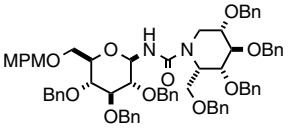
Table 3. Synthesis of various carbamate and urea-linked glycoconjugates



Run	Condition	RCOOH	R′OH/R′NH (*x*)	Product	Time (h)	Yield (%)
1	A	**1**	*t*-BuOH (excess)	 **12**	24	58
2	B	**1**	*t*-BuOH (3)		30	35
3	B[a]	**1**	*t*-BuOH (3)		21	67
4	C	**1**	*t*-BuOH (3)		18	5
5	C	**1**	9-Fm (2)	 **13**	5.5	71
6	D	**1**	9-Fm (2)		3.5	78
7	A	**8**	Tetradecanol (2)	 **14**	5	92
8	C	**8**	 (2)	 **15**	15	94
9	C	**8**	 (3)	 **16**	22	70
10	C	**1**	 **9** (2)	 **17**	8	80
11	A	**1**	 **10** (2)	 **18**	16	64
12	D	**7**	**9** (2)	 **19**	16	81
13	A	**8**	**9** (2)	 **20**	7	86
14	C	**7**	Boc-L-Ser-O*t*-Bu (2)	 **21**	4.5	83
15	A	**8**	Boc-L-Ser-O*t*-Bu (2)	 **22**	13	90
16	A	**8**	HCl·Gly-OEt (2)	 **23**	0.5	93

(*continued on next page*)

Table 3 (*continued*)

Run	Condition	RCOOH	R′OH/R′NH (*x*)	Product	Time (h)	Yield (%)
17	A	**8**	*Z*-L-Lys-OMe·HCl (1.2)	 **24**	1	84
18	A	**8**	 (2)	 **25**	13	82[b]
19	A	**8**	 **11** (1.2)	 **26**	0.5	87

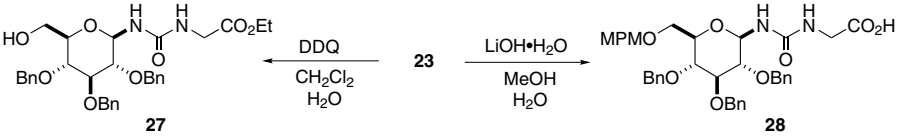
[a] 2 equiv of Ag_2CO_3 was added.
[b] The prereflux to convert RCOOH into RNCO could be omitted.

in the reaction.[8] With K_2CO_3, however, the Fmoc-protected sugar **13** was fortunately obtained in a simple one-pot procedure (run 5), and the yield was improved to 78% with additional catalytic amounts of silver carbonate (run 6).[9] Tetradecanol, cholesterol, and 1-adamatanol reacted with **8** under the modified and unmodified Curtius rearrangement conditions, and the corresponding carbamate-linked glycoconjugates were obtained in 92% yield (run 7, condition A), 94% yield (run 8, condition C), and 70% yield (run 9, condition C), respectively. Compound **14** is thought to be an analog of a glycolipid, and as such examples, various pseudosaccharides, which are linked through a carbamate, would be produced from aglycons under these Curtius rearrangement conditions. Similarly, sugar alcohols **9** and **10** worked as a nucleophile to afford the carbamate-linked disaccharides (runs 10–13). The stereospecific synthesis of both anomeric isomers of disaccharide **19** and **20** could be achieved with the stereoisomers of glycosyl carboxylic acid **7** and **8**.[10] Using an amino acid, Boc-L-Ser-O*t*-Bu as a nucleophile, a carbamate-linked sugar–amino acid complex was successfully obtained: Boc-L-Ser-O*t*-Bu and **7**, **8** were transformed into **21** and **22** in 83% yield by condition C (run 14) and in 90% yield by condition A (run 15), respectively. Judging from the above experiments, the reaction conditions should be chosen as follows: condition A, the general Curtius rearrangement condition in which triethylamine is used as a base, is suitable for reactive carboxylic acids and alcohols (runs 7 and 13 in Table 3). In the case of less reactive carboxylic acids or alcohols, K_2CO_3 should be employed as a base, and additional Ag_2CO_3 is often effective both with triethylamine and K_2CO_3. In some cases, decomposition of substrates or isocyanates by either K_2CO_3 or Ag_2CO_3 is observed, resulting in low yield.

Next, we tried the urea-linked saccharide synthesis by various amines as nucleophiles. Amino acid derivatives, HCl·Gly-OEt and *Z*-L-Lys-OMe·HCl reacted smoothly to give the desired compounds (runs 16 and 17). Compounds **21**, **22**, and **24** are applicable to the synthesis of N- or O-linked glycopeptide analogs. 3-*N*-Benzoylthymine[11] successfully afforded the desired compound **25** in 82% yield (run 18), which would be applied to synthesize nucleic acid derivatives. Azasugar **11**[12] was also utilized as a nucleophile, and urea-linked disaccharide **26** was obtained in 87% yield (run 19).

Then, we investigated further transformation of the neoglycoconjugate. The removal of the MPM group of compound **23** afforded an alcohol (**27**), and also a carboxylic acid (**28**) was obtained by the hydrolysis of **23**. These compounds **27** and **28** will be utilized for elongation of glycoconjugates (Scheme 3).

In summary, we have accomplished a facile synthesis of carbamate- and urea-linked glycoconjugates with sugar carboxylic acids and alcohols or amines by the modified Curtius rearrangement. This reaction is a simple one-pot procedure, and various nucleophiles including tertiary alcohols can be utilized to afford moderate to high yields of desired compounds. And the stereospecific synthesis of the anomeric isomers was also achieved using the corresponding two stereoisomers of glycosyl carboxylic acids. The synthesis and application of more complex neoglycoconjugates are now on-going in our laboratory.



27 **28**

Scheme 3.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.139.

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9. *Typical experimental procedure (Table 3, run 6)*: Compound **1** (44 mg, 0.092 mmol) was refluxed with 9-Fm (36 mg, 0.184 mmol), DPPA (40 μL, 0.184 mmol), triethylamine (25 μL, 0.184 mmol), and silver carbonate (2.5 mg, 0.0092 mmol) in benzene for 3.5 h. The reaction mixture was cooled to at 0 °C, and satdNH_4Claq (20 mL) was added to the reaction mixture, and extracted with ethyl acetate (20 mL) for three times. The combined organic phase was washed with brine and dried with Na_2SO_4. Filtration and evaporation of the organics gave the crude product, which was purified with silica gel chromatography (Wakogel C-300, Wako, hexane/ethyl acetate 6/1–4/1) to give the desired compound **13** in 78% yield: $[\alpha]_D^{19}$ +42.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74–7.76 (2H, m), 7.53–7.55 (2H, m), 7.25–7.40 (19H, m), 5.18 (1H, m, NH), 4.96 (1H, d, $J = 10.7$ Hz), 4.72–4.85 (4H, m), 4.65 (1H, d, $J = 11.2$ Hz), 4.60 (1H, d, $J = 11.9$ Hz), 4.48 (1H, d, $J = 3.4$ Hz), 4.43 (1H, dd, $J = 6.84$, 7.81 Hz); 4.34 (1H, m), 4.20 (1H, m), 4.03 (1H, dd, $J = 9.03$, 9.28 Hz), 3.48 (3H, s), 3.48 (1H, m), 3.25 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.47, 143.57, 143.51, 141.16, 138.41, 137.85, 137.66, 128.43, 128.37, 128.31, 128.23, 127.98, 127.92, 127.88, 127.64, 127.62, 126.96, 124.92, 124.84, 119.90, 127.46, 97.40, 81.13, 79.57, 79.37, 75.92, 75.22, 74.50, 73.36, 66.94, 55.58, 47.03; MS (FAB−NBA+NaI): *m/z* 694 $(M+Na)^+$; HRMS (FAB−NBA+NaI): calcd for $C_{42}H_{41}NNaO_7$, 694.2781; found, 694.2772.
10. The stereochemistries of **19** and **20** were confirmed after removal of their MPM and Bn groups by Pd·C and H_2: ^{1}H NMR of H1′ in **19** (deprotected) (600 MHz, CD_3OD) δ: 5.36 (1H, d, $J = 5.22$ Hz). ^{1}H NMR of H1′ in **20** (deprotected) (600 MHz, CD_3OD) δ: 4.69 (1H, d, $J = 9.07$ Hz).
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