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A Novel Intramolecular Decarboxylative Glycosylation *via* Mixed Carbonate

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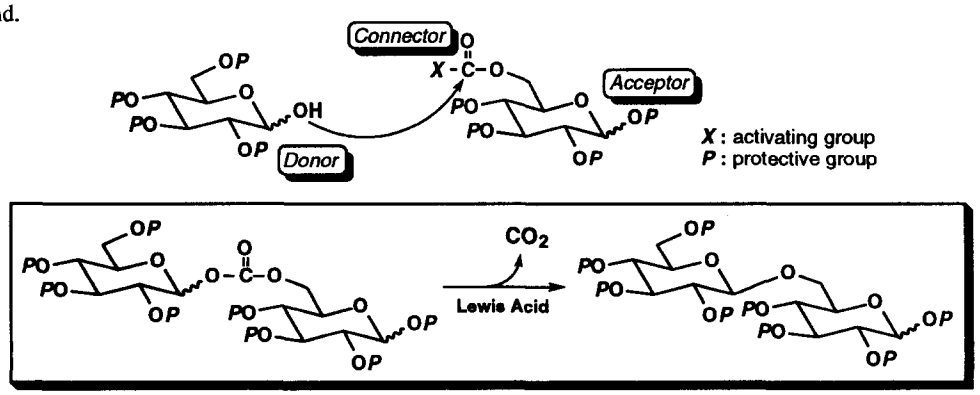
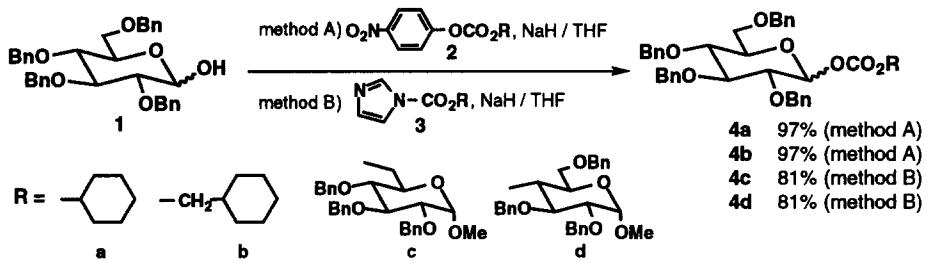
Abstract: A two-step glycosylation procedure, which involves (1) linking two sugars by using carbonate as a connector, (2) removing carbon dioxide to form a glycosidic bond by the aid of Lewis acid, has been developed. This glycosylation procedure was based on the opposite mode of connection, where a glycosyl acceptor was activated to link sugars.

Reflecting increased interest in carbohydrate conjugates with their important biological properties, a large number of methods for the construction of glycosides and oligosaccharides has been developed this past decade. Among them, considerable attention has been directed toward the efficient formation of interglycosidic linkages.[1] The glycosidic bond formation in saccharides synthesis is generally based on the activation of glycosyl donors with appropriate leaving groups using promoters, but employment of activated glycosyl acceptors to connect sugars seems to be an attractive alternative because it might provide flexible strategies for the construction of oligosaccharides.[2] Schmidt and co-workers have reported 1-*O*-alkylations of carbohydrates based on this concept.[3] However, their reports suggested difficulty in application of their method to the complex saccharides. Along this line, we explored a two-step procedure in which an activated glycosyl acceptor was employed to connect sugars in the first step. The glycosylation procedure disclosed herein involves linking two sugar moieties using carbonate as a connector and removing internal carbon dioxide by the aid of Lewis acid to form a glycosidic bond.



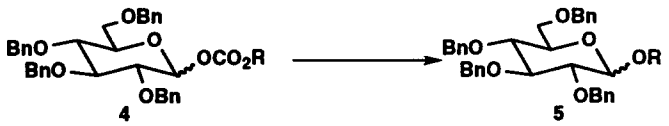
In principle, mixed carbonates might be prepared by treating alcohols with chloroformates (activating group X = Cl). However, the chloroformates are unstable and phosgene is used in their preparation. Scattered reports on other mixed carbonate formations prompted us to develop efficient reaction conditions applicable to the first step of our glycosylation protocol. Scanning activated carbonates, we found 4-nitrophenyl carbonate (activating group X = 4-nitrophenoxy) and imidazolide (X = imidazolyl)[4] to be good candidates because of their moderate reactivity to connect two different alcohols sequentially. In fact, reaction of benzyl protected glucopyranose **1** with alkyl 4-nitrophenyl carbonate (**2a** or **2b**)[5] in the presence of NaH in THF (method A) afforded mixed carbonate (**4a** or **4b**) as a mixture of anomers (α : β = 1 : 1 - 1 : 2) in high yield as shown in Scheme 1. Preparation of **4c** or **4d** by using 4-nitrophenyl carbonate (**2c** or **2d**), however, required tedious chromatographic separation to remove a by-product (bis(4-nitrophenyl) carbonate). In these cases, imidazolide (**3c** or **3d**)[5] was successfully used in place of 4-nitrophenyl carbonate to obtain the desired products (method B).

With mixed carbonates in hand, we next examined the intramolecular decarboxylative glycosylation reaction. Alkyl aryl carbonates have been reported to afford the corresponding alkyl aryl ethers on pyrolysis with evolution



Scheme 1

Table 1. Decarboxylative Glycosylation Promoted by Trialkylsilyl Triflate.[a]



Entry	R	Solvent	Promoter: TMSOTf Yield (%)	TMSOTf α : β[b]	TBDMSOTf Yield (%)	TBDMSOTf α : β[b]
1	a	CH_2Cl_2	81	41 : 59	75	32 : 68
2	a	propionitrile	0	-	0	-
3	a	toluene	85	32 : 68	73	19 : 81
4[c]	a	toluene	80	35 : 65	69	19 : 81
5	a	mesitylene	75	23 : 77	69	20 : 80
6	b	toluene	76	16 : 84	75	25 : 75
7	b	mesitylene	70	16 : 84	74	29 : 71
8	c	toluene	79	32 : 68	85	28 : 72
9	c	mesitylene	78	16 : 84	72	16 : 84
10	d	toluene	67	42 : 58	67	36 : 64
11	d	mesitylene	72	37 : 63	62	31 : 69

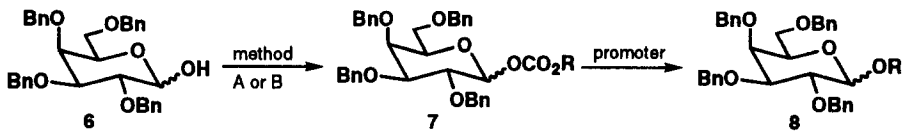
[a] The reaction was carried out in the presence of trialkylsilyl triflate (1.1 equiv.) at 0 °C for 30 min. [b] Determined by HPLC analysis. [c] Partially separated carbonate **4a** having a different anomeric ratio (α : β = 5 : 1) was used in place of **4a** (α : β = 1 : 1).

of carbon dioxide.[6] Ishido and co-workers have applied this decarboxylation to the conversion of 1-*O*-phenoxycarbonyl glucopyranose into phenyl glucopyranoside.[7] Considering the mechanism of this transformation reaction, we presumed that intramolecular decarboxylative glycosyl bond formation might be promoted by an appropriate activation of carbonate at lower temperature. From this point of view, we studied the evolution of carbon dioxide and formation of a glycosidic bond mediated by Lewis acids.

Surveying promoters for the decarboxylative conversion of **4a** into **5a**, we found trimethylsilyl triflate (TMSOTf) and *t*-butyldimethylsilyl triflate (TBDMSOTf) to be effective. Some other Lewis acids (BF_3·OEt_2, $SnCl_4$, $ZnCl_2$ and $Zn(OTf)_2$) also promoted the glycosylation, but yields were lower (20 - 60%) than that obtained by the trialkylsilyl triflates. It is noteworthy that the choice of solvent was crucial to obtain high yield with β-stereoselectivity as shown in Table 1. For example, in propionitrile which is often used for the glycosylation reaction, the reaction did not proceed at all. Interestingly, a remarkable solvent effect of mesitylene on the stereoselectivity was found in these reactions.[8] In this reaction, yield and stereoselectivity were not affected by the stereochemistry of the starting carbonate that was shown by using a different anomeric ratio of carbonate (entry 4 in Table 1).[9] In the other substrates (**4b**, **4c**, and **4d**), the decarboxylative glycosylation promoted by TMSOTf or TBDMSOTf afforded the desired glycosylated products (**5b**, **5c**, and **5d**) in *ca.* 70 - 85% yield (Table 1). The stereoselectivity was altered by changing the promoter and solvent, the appropriate combination of which produced β-anomer predominantly (α : β = *ca.* 1 : 4 - 1 : 5; underlined in Table 1) except the mixed carbonate of a sterically hindered secondary alcohol (α : β = *ca.* 1 : 2; entry 10 and 11 in Table 1).

Application of this glycosylation procedure to galactopyranose 1-carbonates **7** is summarized in Table 2. The glycosides **8a** - **8d** (R: see Scheme 1) were similarly obtained from galactopyranose **6** in 2 steps. The stereoselectivity observed in galactopyranosides **8** was somewhat confusing compared with that of glucopyranoside **5**. TBDMSOTf as a promoter or mesitylene as a solvent, both of which increased β-selectivity in the case of **5**, had the ability to enhance α-selectivity. The rationale for the curious stereoselectivity observed here has not been elucidated, but the location of the 4-benzyloxy group on the pyranose ring, which can interact with Lewis acid (trialkylsilyl triflate), might play an important role in determining the stereochemical outcome of this reaction.

Table 2. Decarboxylative Glycosylation of Galactosyl Carbonate



	Carbonate formation		Glycosylation[a]			
			Promoter : TMSOTf		TBDMSOTf	
Substrate[b]	Method[c]	Yield (%)	Yield (%)	α : β[d]	Yield (%)	α : β[d]
7a	A	91	72	40 : 60	65	72 : 28
			(68)	(53 : 47)	(71)	(67 : 33)
7b	A	89	70	37 : 63	77	70 : 30
			(73)	(67 : 33)	(65)	(73 : 27)
7c	B	75	83	46 : 54	62	62 : 38
7d	B	52	69	42 : 58	72	34 : 66

[a] The reaction was carried out in the presence of trialkylsilyl triflate (1.1 equiv.) at 0 °C for 30 min in toluene (or mesitylene: shown in parthensis). [b] R: see Scheme 1. [c] Methods A and B: see Scheme 1. [d] Determined by HPLC analysis.

The glycosylation reaction for the synthesis of complex oligosaccharides requires high yield with high stereoselectivity. The intramolecular decarboxylative glycosylation presented herein has not attained this goal yet, but it may enroll a new synthetic plan in the area of oligosaccharide synthesis because an opposite mode of attachment of sugars is utilized in this process. The greatest advantage of this glycosylation procedure over others is that the glycosyl donor part can be used without attaching a leaving group and extension of this ability to an oligosaccharide synthesis is under investigation in this laboratory.

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5. Nitrophenyl carbonates **2** or imidazolides **3** were obtained by reactions of corresponding alcohols with commercially available 4-nitrophenyl chloroformate with triethylamine or carbonyldiimidazole respectively.
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8. Narasaka has reported similar solvent effects on enantioselectivity in asymmetric pericyclic reactions: (a) Narasaka, K.; Inoue, M.; Yamada, T.; Sugimori, J.; Iwasawa, N. *Chem. Lett.* **1987**, 2409. (b) Narasaka, K.; Hayashi, Y.; Shimada, S. *Chem. Lett.* **1988**, 1609.
9. Contrary to the benzyl protected glucopyranose 1-carbonate, only β-anomer of benzoyl protected glucopyranose 1-carbonate reacted under similar conditions to afford β-glycoside with α-anomer of the carbonate unchanged. Ishido and co-workers have reported similar different reactivity between α- and β-anomers of carbonate.[7] We are now investigating β-selective carbonate formation of acyl protected sugars and their decarboxylative glycosylation.

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