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An Efficient Synthesis of Mixed β-Carbonates of Acyl-Protected Sugar and Their Decarboxylative Glycosidation Promoted by Trimethylsilyl Trifluoromethanesulfonate

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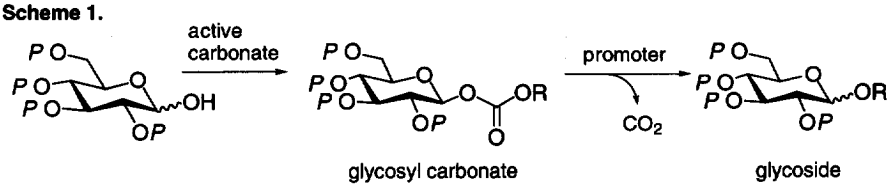
Abstract: Mixed β-carbonates of acyl-protected sugar are stereoselectively prepared by using an *N*-succinimidyl group for activation of the acceptor alcohol carbonate. The glycosyl carbonates are smoothly decarboxylated by trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) to give β-glycosides preferentially in high yields.

Keywords: carbonates; decarboxylation; glycosidation; neighbouring group effects

Stereoselective construction of glycoconjugates is still an important problem in organic chemistry. Various leaving groups, promoters and conditions have been investigated in order to control the stereochemistry of an anomeric carbon in glycosidation reactions.[1] In these prevailing methods, the obtained glycosides are sometimes accompanied by by-products derived from a leaving group or a promoter. To reduce these undesired products, it is desirable that the residue of a leaving group should be removed from the reaction mixture as the reaction proceeds. In this point of view, we have developed the decarboxylative glycosidation via mixed carbonate. A carbonate is one of the most effective leaving groups used for activation of the anomeric carbon,[2-5] and there are two approaches which use carbonate for donor activation. One is that the carbonate is used as just a leaving group[2] independent from the acceptor alcohol and the other is that the donor sugar is linked with the acceptor alcohol as a carbonate before glycosyl bond formation, which also acts as a cap of the acceptor alcohol (Scheme 1).[3-5]

Scheme 1.



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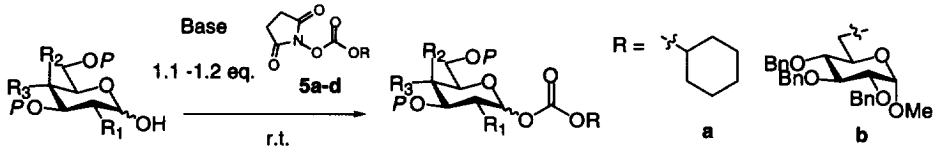
Recently, we were successful in the latter method resulting in the β-preferential glycosidation of 2-*O*-benzyl-protected sugar carbonates promoted by a stoichiometric amount of Me_3SiOTf[4a] and in the α-preferential glycosidation by a combination of a catalytic amount of a Lewis acid and silver(I) perchlorate as a promoter.[4b] Lately, that the former reaction proceeds intermolecularly was published by Schmidt et. al.[5] It is considered that the selectivity might be mainly controlled by both the solvent effect and the nature of the metal cation-acceptor alcohol complex. Another promising way to control the stereoselectivity of glycosidation reaction is the neighboring group participation of an acyl group at the 2-*O*-position of the donor sugar,[1d] which could be expected as high β-selectivity. We report here the β-selective decarboxylative glycosidation of acyl-protected sugar carbonates promoted by Me_3SiOTf, and the selective synthesis of the mixed β-carbonates which are needed for their easier decarboxylation.

In a preliminary experiment, when the α-anomer of 2,3,4,6-tetra-*O*-benzoylglucopyranos-1-yl cyclohexyl carbonate was treated with a stoichiometric amount of Me_3SiOTf, the unreacted α-carbonate was recovered with slight decomposition, while the β-anomer gave the corresponding glucoside under the same conditions.[6] Therefore, highly selective synthesis of β-carbonates was required in this decarboxylative glycosidation. To our best knowledge, however, there is

Table 1. Synthesis of Various Glycosyl Carbonate



Glc: R_1 = O*P*, R_2 = H, R_3 = O*P*
1 *P* = Bz, **2** *P* = Piv
Gal: R_1 = O*P*, R_2 = O*P*, R_3 = H
3 *P* = Piv
GlcN: R_1 =NPhth, R_2 = H, R_3 = O*P*
4 *P* = Ac

Piv: Pivaloyl
Phth: Phthaloyl

Entry	Donor Sugar	R	Base (eq)	Solvent	Time	Product	Yield (%)	α:β[a]
1	**1**	**a**	K_2CO_3 (3.0)	toluene	20 h	**6**	97	<1:>99
2	**1**	**a**	K_2CO_3 (3.0)	CH_2Cl_2	44 h	**6**	92	4:96
3	**1**	**b**	K_2CO_3 (1.1)	toluene	26 h	**7**	88	<1:>99
4	**1**	**c**	K_2CO_3 (1.1)	toluene	10 d	**8**	79	<1:>99
5[b]	**1**	**c**	K_2CO_3 (1.1)	toluene	16 h	**8**	79	4:96
6	**2**	**a**	K_2CO_3 (3.0)	toluene	20 h	**9**	90	2:98
7	**2**	**b**	K_2CO_3 (1.1)	toluene	44 h	**10**	92	3:97
8	**2**	**c**	K_2CO_3 (3.0)	toluene	9 d	**11**	56	3:97
9	**2**	**c**	NaH (1.1)	toluene	4 h	**11**	86	<1:>99
10	**3**	**a**	K_2CO_3 (3.0)	toluene	4 d	**12**	81	6:94
11	**3**	**b**	K_2CO_3 (3.0)	toluene	20 h	**13**	79	4:96
12	**3**	**c**	K_2CO_3 (3.0)	toluene	5 d	**14**	56	3:97
13	**3**	**c**	NaH (1.1)	toluene	24 h	**14**	82	<1:>99
14	**4**	**a**	K_2CO_3 (3.0)	CH_2Cl_2	15 h	**15**	89	<1:>99
15	**4**	**d**	K_2CO_3 (3.0)	CH_2Cl_2	40 h	**16**	76	<1:>99

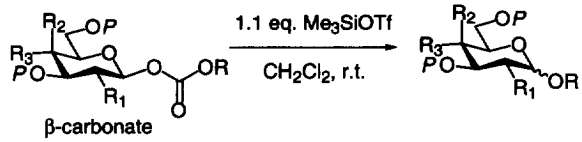
[a] The α:β ratio was determined by ^1H NMR. [b] Reaction was performed at 60 °C.

no report on a general stereoselective synthesis of the 1-*O*-acyl derivatives of 2-*O*-acyl protected sugar which would be essential as model reactions of 1-*O*-oxycarbonylation.[7]

The use of a succinimidyl group[8] as an activating group was the most effective for the synthesis of the mixed β-carbonates of 2,3,4,6-tetra-*O*-benzoyl or 2,3,4,6-tetra-*O*-pivaloyl-D-glucopyranose and the reactions in the presence of K_2CO_3 in toluene gave the optimal results of excellent β-selectivity in high yield (Table 1, Entry 1, 6).[9-11] Dichloromethane was also effective as a solvent, though slightly lower yield and selectivity were observed (Entry 2). These conditions were applicable to the mixed carbonate synthesis of various acyl-protected glycosyl donors and benzyl-protected acceptor sugars (Entry 3, 4, 7, 8, 11, 12). Some cases using NaH instead of K_2CO_3 gave better yields in making the 1-4 linkage (Entry 9, 13). The β-anomers of *N*-phthaloyl-D-glucosamine carbonates could also be synthesized in good yields under the same conditions but in CH_2Cl_2 (Entry 14, 15) because of the insolubility of the donor sugar in toluene. All pure β-carbonates could be obtained by recrystallization or chromatographical purification, and stored without any decomposition at room temperature.

These β-carbonates (**6-16**) were smoothly decarboxylated by the use of 1.1 equimolar amount of Me_3SiOTf without any additives in CH_2Cl_2 to give the corresponding β-glycosides (**17-27**) with high stereoselectivity in high yield (Table 2).[12] In the case where the acceptor alcohol is cyclohexanol (Entry 1-3, 6, 9), the expected anomerization of β-glycoside was observed to some extent, that is, the ratio of the α-anomer increased gradually during the reaction course (Entry 1-3).

Table 2. Decarboxylative Glycosidation Promoted by Me_3SiOTf



Entry	Mixed Carbonate	Reaction Time (h)	Glycoside	Yield[a]	α:β ratio[b]
1	**6**	0.5	**17**	56	3:97[c]
2	**6**	2.0	**17**	83	6:94[c]
3	**6**	3.0	**17**	85	10:90[c]
4	**7**	1.0	**18**[d]	89	<1:>99
5	**8**	2.0	**19**[d]	81	<1:>99
6	**9**	1.2	**20**	90	3:97[c]
7	**10**	1.5	**21**[d]	91	<1:>99
8	**11**	2.0	**22**[d]	76	<1:>99
9	**12**	1.0	**23**	87	2:98[c]
10	**13**	1.0	**24**	86	<1:>99
11	**14**	1.5	**25**	63	<1:>99
12	**15**	3.0	**26**[e]	74	<1:>99
13	**16**	3.0	**27**[e]	72	<1:>99

[a] Isolated yield of a mixture of α- and β-anomers. [b] The ratio of anomers was determined by ^1H NMR analysis. [c] ^1H NMR spectrum of each anomer is coincident with that of the authentic compound. [d] ^1H and ^{13}C spectra of β-anomer were coincident with those in literature: **18**: ref. 13, 14; **19**: ref. 13, 15; **21**: ref. 16; **22**: ref. 17. [e] The glycosides were fully characterized by their ^1H, ^{13}C NMR and HRMS spectral data.

A plausible mechanism for the decarboxylative glycosidation involves an initial activation

of a carbonate moiety with Me_3SiOTf to afford cyclic acyloxonium trifluoromethanesulfonate as explained for other glycosidations and trimethylsilyl ether of the acceptor alcohol with accompanying evolution of carbon dioxide. The cyclic acyloxonium ion would then couple with the trimethylsilyl ether of the acceptor alcohol to form the β-glycoside. The details of the reaction mechanism and the kinetics are now under investigation.

In conclusion, a highly β-selective formation of glycosyl carbonates using an *N*-succinimidyl group and a highly β-selective decarboxylative glycosidation reaction promoted by Me_3SiOTf were developed.

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References and Notes

† Deceased on May 16, 1997.

[1] Recent reviews: (a) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095-1121. (b) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503-1531. (c) Schmidt, R. R. *Pure & Appl. Chem.* **1989**, *61*, 1257-1270. (d) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155-173.

[2] (a) Boursier, M.; Descotes, G. *C. R. Acad. Sci.* **1989**, *308*, 919-921. (b) Ford, M. J.; Ley, S. V. *Synlett* **1990**, 255-256. (c) Marra, A.; Esnault, J.; Veyriéres, A; Sinäy, P. *J. Am. Chem. Soc.* **1992**, *114*, 6354-6360. (d) Mukaiyama, T.; Sasaki, T.; Iwashita, E.; Matsubara, K. *Chem. Lett.* **1995**, 455-456. (e) Mukaiyama, T.; Miyazaki, K.; Uchiro, H. *Chem. Lett.* **1998**, 635-636.

[3] (a) Inaba, S.; Yamada, M.; Yoshino, T.; Ishido, Y. *J. Am. Chem. Soc.* **1973**, *95*, 2062-2063. (b) Ishido, Y.; Inaba, S.; Matsuno, A.; Yoshino, T.; Umezawa, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1382-1390.

[4] (a) Iimori, T.; Shibazaki, T.; Ikegami, S. *Tetrahedron Lett.* **1996**, *37*, 2267-2270. (b) Iimori, T.; Azumaya, I.; Shibazaki, T.; Ikegami, S. *Heterocycles* **1997**, *46*, 221-224.

[5] Scheffler, G.; Schmidt, R. R. *Tetrahedron Lett.* **1997**, *38*, 2943-2946.; We have also observed similar evidence independently, which will be published in due course.

[6] We have preliminary results that both α- and β-carbonate could be promoted by 0.2 eq of $Hf(OTf)_4$ to give glycosides. This will provide a flexible strategy for oligosaccharide synthesis using the decarboxylative glycosidation.

[7] Glycoesters of 2-*O*-benzyl protected sugars could be stereoselectively synthesized under various conditions.: see (a) Shoda, S., Mukaiyama, T. *Chem. Lett.* **1982**, 861-862. (2) Bols, M.; Hansen, H. C. *Acta Chem. Scand.* **1993**, *47*, 818-822.

[8] (a) Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1964**, *86*, 1839-1842. (b) Ghosh, A. K.; Duong, T. T.; McKee, S. P.; Thompson, W. J. *Tetrahedron Lett.* **1992**, *33*, 2781-2784. (c) Pereira, D.; Hai, T. T.; Nelson, D. *Synth. Commun.* **1998**, *28*, 4019-4024.

[9] The amount of K_2CO_3 (1.1 - 3.0 mol/mol) does not essentially affect the reaction time, yield and selectivity, but it might remove slight water if it remained in the reaction mixture.

[10] Typical procedure for *N*-succinimidyloxycarbonates (**5a-d**): To a solution of acceptor alcohol (1 mmol) and disuccinimidyl carbonate (1.1 - 2.0 mmol) in acetonitrile (5 mL) was slowly added triethylamine. The reaction mixture was stirred at ambient temperature for 3 h - 6 days. After usual working up, the crude product was purified by silica gel column chromatography to give pure *N*-succinimidyloxycarbonates in 83 - 92 % yields. The analytical data for *N*-succinimidyloxycarbonate and mixed sugar carbonate will be reported elsewhere.

[11] Typical procedure for glycosyl carbonates: To a solution of donor sugar (1 mmol) and *N*-succinimidyloxy carbonate (1.2 mmol) in toluene (10 mL) was added K_2CO_3 (3 mmol) in one portion. The reaction mixture was stirred at ambient temperature. After usual working up, the crude product was purified by silica gel column chromatography. Pure β-anomer was obtained after purification by silica gel column chromatography. ^1H NMR (anomeric proton; at 400 MHz; in $CDCl_3$ with TMS as an internal standard) for pure β-anomer: **6**: δ 5.99 (d, J = 7.9 Hz); **7**: δ 5.97 (d, J = 8.0 Hz); **8**: δ 6.01 (d, J =8.2 Hz); **9**: δ 5.63 (d, J = 8.2 Hz); **10**: δ 5.60 (d, J = 8.2 Hz); **11**: δ 5.60 (d, J = 8.2 Hz); **12**: δ 5.65 (d, J = 8.5 Hz); **13**: δ 5.62 (d, J = 8.2 Hz); **14**: δ 5.62 (d, J = 8.2 Hz); **15**: δ 6.42 (d, J = 8.9 Hz); **16**: δ 6.47 (d, J = 8.9 Hz).

[12] Typical procedure for decarboxylative glycosidations: To a solution of a pure β-anomer of glycosyl carbonate in CH_2Cl_2 was slowly added a solution of Me_3SiOTf (1.1 eq) in CH_2Cl_2 (0.1 M) at -30 °C. The reaction mixture was then stirred at 0 °C for 1 - 3 h. After usual working up, the crude product was purified by silica gel column chromatography. The yield was severely lowered by a slight amount of water. Use of catalytic Me_3SiOTf resulted in the glycoside along with decomposed products due to a longer reaction time.

[13] Hashimoto, S.; Sano, A.; Umeo, K.; Nakajima, M.; Ikegami, S. *Chem. Pharm. Bull.* **1995**, *43*, 2267-2269.

[14] (a) Hashimoto, S.; Honda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1989**, 685-687. (b) Fukase, K.; Hasuoka, A.; Kinoshita, I.; Aoki, Y.; Kusumoto, S. *Tetrahedron* **1995**, *51*, 4923-4932.

[15] Dasgupta, F.; Garegg, P. J. *Carbohydr. Res.* **1988**, *177*, c13-c17.

[16] Böhm, G.; Waldmann, H. *Liebigs Ann. Chem.* **1996**, 621-625.

[17] Chenault, H. K.; Castro, A.; Chafin, L. F.; Yang, J. *J. Org. Chem.* **1996**, *61*, 5024-5031.