Regioselective Acylation of Carbohydrates with 1-Acyloxy-1*H*-benzotriazoles

István F. Pelyvás,*[1] Thisbe K. Lindhorst, Harald Streicher, Joachim Thiem
Institut für Organische Chemie, Universität Hamburg, Martin-Luther-King-Platz 6, D-2000 Hamburg 13, Germany

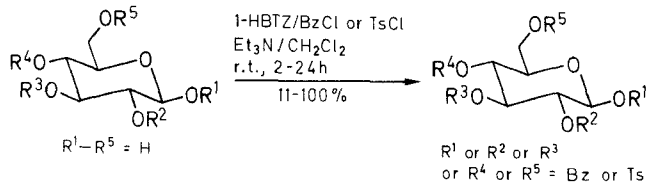
Acylation of representative carbohydrate derivatives was accomplished with in situ generated 1-acyloxy-1*H*-benzotriazoles. The observed high regioselectivity, mild reaction conditions and convenient work-up make the presented one-pot procedure generally applicable and more advantageous than acylations with previously introduced reagents, including *N*-acylimidazoles.

Selective acylations of carbohydrate derivatives with a variety of acylating agents have been studied for a long time and comprehensively reviewed.[2,3] However, many of the reagents employed are reported to possess insufficient regioselectivity, and sometimes the procedures involve either low-temperature operations or forced conditions and long reaction time (i.e. in the case of *N*-acylimidazoles[4,5]).

A simple procedure for the selective benzoylation of polyols with 1-benzoyloxy-1*H*-benzotriazole (1-BBTZ)[6] was previously reported by Kim et al.[7] Among noncarbohydrate diols, the 4,6-*O*-benzylidene derivatives of methyl α-D-glucopyranoside and methyl α-D-altropyranoside could be regioselectively benzoylated with 1-BBTZ at OH-2, whereas in the case of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside, an approximately 1:1 mixture of the 2-*O*- and 3-*O*-benzoates was produced, with the isolated reagent.

The present paper extends and simplifies this acylation procedure for diversely protected carbohydrates **1, 5, 7, 9, 11, 14, 16, 19, 22, 25, 28, 30** and **31** in a convenient one-pot operation.

The acylation experiments were performed at room temperature by in situ generation of the 1-acyloxy-1*H*-benzotriazoles (hereafter referred as 1-BBTZ or 1-TBTZ) from 1-hydroxy-1*H*-benzotriazole (1-HBTZ) and benzoyl- or tosyl chloride in the presence of an equimolar quantity of triethylamine, followed by simultaneous addition of a solution of the sugar and a second equivalent of triethylamine. The applied reaction conditions and physical data of the products are summarized in Table 1 and the most characteristic ^{1}H-NMR data in Table 2.



TLC investigation of the mixture produced upon benzoylation of methyl α-D-glucopyranoside (**1**) with 3.3 equivalents of 1-BBTZ showed the major product to be methyl 2,4,6-tri-*O*-benzoyl-α-D-glucopyranoside (**3**), accompanied by 2,3,6-tri-*O*-benzoate **4** and traces of the tetra-*O*-benzoate **2**. Column chromatography yielded approximately 40% of pure **3** along with 16% of **4** and a mixture of **3** and **4** with significant preponderance of the 2,4,6-tri-*O*-benzoate **3**. Thus, contrary to benzoylations of **1** with benzoyl chloride[8,9] or with *N*-benzoylimidazole,[10] where 2,3,6-tri-*O*-benzoate **4** was the main product, the application of this new reagent allows a facile access of preparative quantities of the 2,4,6-tri-*O*-benzoate **3** by direct benzoylation.

Allyl 2-*O*-benzoyl-α-D-glucopyranoside (**5**) could be selectively benzoylated at the primary hydroxy group upon benzoylation with one equivalent of 1-BBTZ to give the 2,6-di-*O*-benzoate **6**, a useful intermediate in natural products syntheses,[11,12] in 81% yield. Tosylation of allyl 6-*O*-(tert-butyldimethylsilyl)-α-D-glucopyranoside (**7**) with two equivalents of 1-tosyloxy-1*H*-benzotriazole (1-TBTZ) resulted in 48% of the 2-*O*-tosylate **8**. The failure of the reaction to go to completion, and the lack of tosylation at the other secondary hydroxy groups may be a result of steric hindrance due to the bulky silyl ether function at O-6. A similar effect may be in operation in the case of the 2-deoxy-6-*O*-silyl glycoside **14**, affording, exclusively, the 3-*O*-tosylate **15** in 66% yield, whereas the lack of the large silyl group in methyl 2,6-dideoxy-α-L-*arabino*-hexopyranoside (**16**) resulted in an approximately 1:1 mixture of the 3-*O*- (**17**) and 4-*O*-tosylate (**18**).

Most surprisingly, an analogous benzoylation of methyl β-D-glucopyranoside (**9**) with 3 equivalents of 1-BBTZ gave neither the tetra-*O*-benzoate nor any of the tri-*O*-benzoates. Instead, the reaction mixture comprised approximately 30% of the unreacted **9** along with an approximately 8:1 mixture of two di-*O*-benzoates. Column chromatography allowed the separation of the major product, the hitherto unknown methyl 3,6-di-*O*-benzoyl-β-D-glucopyranoside (**10**) in 60% yield. The substitution pattern in **10** was unequivocally proved by ^{1}H-NMR spin decoupling experiments to assign the chemical shift of H-3 and H-2 at $\delta = 5.22$ and $\delta = 3.65$, respectively. On the contrary, either the conventional[13] or the stannylidene-assisted[9] direct benzoylations of the corresponding α-anomer **1** gave methyl 2,6-di-*O*-benzoyl-α-D-glucopyranoside. Consequently, selection of the configuration of the anomeric protecting group offers a distinction to obtain either the 2,6-di-*O*- or 3,6-di-*O*-benzoate in the glucose series, both of which are appropriate starting materials for oligosaccharide syntheses.

The higher reactivity of the anomeric hydroxy group towards 1-BBTZ is demonstrated by the benzoylation of **11** which leads to **12** in addition to fully protected **13**. Further, the method can also be applied to unprotected pyranoses, such as L-fucose (**19**), to give the 1,3-di-*O*-benzoyl- (**20**) and 1,2,3-tri-*O*-benzoyl-β-fucopyranose (**21**). The comparatively low yield of 32% for the preparation of **20** from L-fucose is not too bad since a selective approach to a fucose derivative such as **20** could otherwise only be achieved by multi-step synthesis. On the other hand, the synthesis of a 1,2,3-tri-*O*-benzoyl-protected fucose derivative proceeds more conveniently in a classical low temperature benzoylation.[14] Thus the order of reactivity of the hydroxy groups for fucose in

Table 1. Regioselective Acylation of Cabohydrate Derivatives

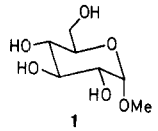
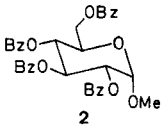
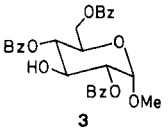
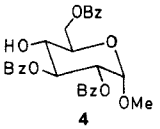
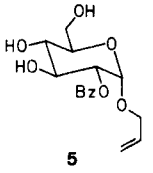
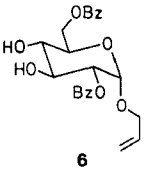
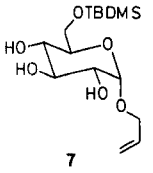
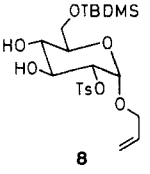
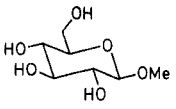
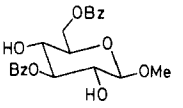
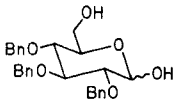
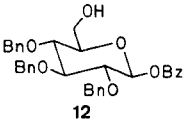
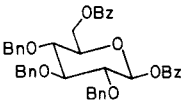
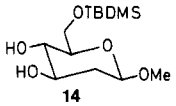
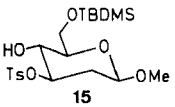
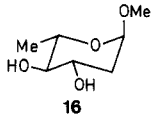
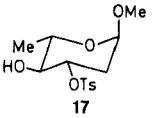
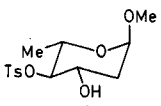
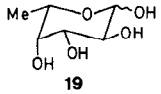
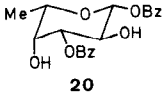
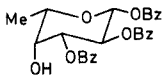
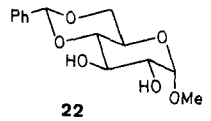
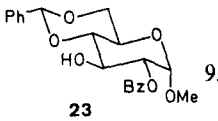
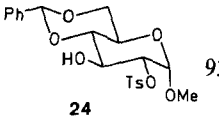
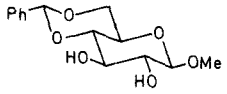
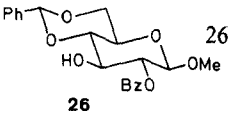
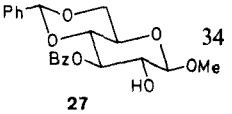
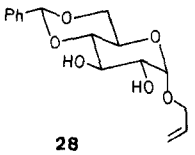
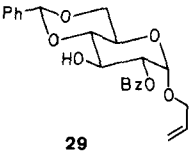
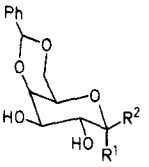
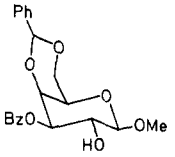
Substrate	Reaction Conditions Reagent/ Equiv	Time (h)	Solvent[k]	Product	Yield (%)	mp (°C)	$[\alpha]_D^{25}$ (c, $CHCl_3$)	Molecular Formula[a] or Lit. mp (°C)/ $[\alpha]_D$ ($CHCl_3$)
 1	1-BBTZ/3.3	24	A	 2	2	107–108	+82 (1.2)	106–108[10]/+84[20]
				 3	40	syrup	+101 (1.1)	+99[10]
				 4	16	130.5	+144 (1.2)	127–129[9]/+149.4[9]
 5	1-BBTZ/1.1	5	B	 6	81	136–137	+74 (1.0)	+74[12]
 7	1-TBTZ/2.2	4[b]	C	 8	48	syrup	+65 (1.8)	$C_{32}H_{36}O_8SSi$ (608.8)
 9	1-BBTZ/3.3	2; 22[c]	D, E	 10	60	140–142	+14 (1.0)	$C_{21}H_{22}O_7$ (386.4)
 11	1-BBTZ/1.1	18[d]	F	 12	52	115–116	−26 (1.0)	$C_{34}H_{34}O_7$ (554.6)
				 13	20	syrup	−1.0 (2.7)	$C_{41}H_{38}O_8$ (658.7)
 14	1-TBTZ/1.1	22[f]	G, K	 15	66	syrup	−20 (1.0)	$C_{20}H_{34}O_7SSi$ (446.6)
 16	1-TBTZ/1.1	24	H	 17	78[g]	syrup	−95 (2.1)	−116[21]
				 18				
 19	1-BBTZ/1.1	2.5	I	 20	32	syrup	−17 (2.1)	$C_{20}H_{20}O_7$ (372.4)
				 21	11	syrup[h]	–	$C_{24}H_{24}O_8$ (440.4)

Table 1. (continued)

Substrate	Reaction Conditions Reagent/ Equiv	Time (h)	Solvent[k]	Product	Yield (%)	mp (°C)	$[\alpha]_D^{25}$ (c, $CHCl_3$)	Molecular Formula[a] or Lit. mp (°C)/ $[\alpha]_D$ ($CHCl_3$)
 **22**	1-BBTZ/1.1	24	J	 **23**	95	168–170	+108 (1.0)	169–170[7]/+107[7]
	1-TBTZ/1.1	16	K	 **24**	93	153–155	+64 (1.0)	153.5–155[17]/+64[22]
 **25**	1-BBTZ/1.1	24[i]	J	 **26**	26	201–202	−34 (1.0)	198–199[7]/−33[7]
				 **27**	34	180–182	−106 (1.2)	180–182[7]/−106.5[7]
 **28**	1-BBTZ/1.1	16[j]	C	 **29**	75	syrup	+110 (1.0)	+110[12]
 **30** R^1 = OMe, R^2 = H **31** R^1 = H, R^2 = OMe	1-BBTZ/1.1	18	K	 **32**	100	166–167	+95 (1.1)	165[23]/+95[23]

[a] If not otherwise noted, satisfactory microanalyses obtained: C ±0.35, H ±0.15.
[b] Starting material (~20%) is present even after 20 h.
[c] Starting material (~30%) is present even after 22 h.
[d] Starting material (~20%) remains unreacted.
[e] Prepared from methyl 2-deoxy-β-D-*arabino*-hexopyranoside[24] by reaction with *tert*-butyldimethylsilyl chloride in pyridine; mp 88°C; $[\alpha]_D^{25}$ −62° (*c* = 1.2, $CHCl_3$).
[f] Starting material (~10%) remains unreacted.
[g] A 1:1 mixture of **17** and **18**, not separable.
[h] Compound **21** is identified only by its ^{1}H-NMR spectrum.
[i] Starting material (~25%) remains unreacted.
[j] Starting material (~10%) remains unreacted.
[k] For chromatography see experimental section.

chemical benzoylation showed to be 1-OH > 3-OH > 2-OH > 4-OH. Corresponding acylations also proved to be a rather useful method for other cases of selective protection of 6-deoxy-sugars.[15]

In agreement with findings reported by Kim et al.[7] analogous benzoylation with one molar equivalent of 1-BBTZ of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **(22)** and of the corresponding allyl glucoside **28** proceeded with excellent regioselectivity to afford the respective 2-*O*-benzoates **23** and **29** in 95% and 75% isolated yield, respectively. Tosylation of **22** with one molar equivalent of the in situ generated 1-TBTZ showed similar high selectivity, allowing the isolation of 93% of the 2-*O*-tosylate **24**. In comparison, benzoylation[16] and tosylation[17] of **22** with *N*-benzoyl- and *N*-tosylimidazole in chloroform at reflux temperature for several hours gave only 78% of **23** and **24**, respectively, and benzoylation of **22** with benzoyl cyanide afforded[3] the 2-*O*-benzoate **23** in 62% yield.

At the same time, no selectivity of the benzoylation of the β-anomer **(25)** of **22** with 1-BBTZ was observed, and an approximately 1:1 mixture of the two monobenzoates **26** and **27** was isolated. Similarly, benzoylation of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside **(30)** resulted in the formation of the two monobenzoates in a nearly 1:1 ratio. Contrarily, the corresponding β-anomer **31** of **30** showed superior regioselectivity and gave the 3-*O*-benzoate **23** in a near quantitative yield. This observation demonstrates the advantages of the present procedure, since e.g. **31** gives only 65% and 47–58% of the *O*-3 esters upon conventional acylation with ethoxycarbonyl chloride[18] and tosyl chloride.[19]

The results detailed above clearly prove the general utility of 1-acyloxy-1*H*-benzotriazoles in regioselective acyl-

Table 2. Characteristic ^{1}H-NMR Data of Acylated Carbohydrates Prepared [$CDCl_3$/TMS, δ, J (Hz)]

Compound	H-1	H-2	H-3	H-4	H-5	H-6	H-6′	OCH_3	H_{arom}	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5',6'}$	$J_{6,6'}$
2	5.30	5.36	6.22	5.72		4.40–4.70		3.50	7.28–8.15	3.7	10.5	10.0	10.0	–	–	–
3	5.05–5.18		4.50	3.38		4.25–4.65		3.48	7.25–8.15	–	–	9.5	9.5	–	–	–
4	5.15	5.28	5.80	3.88	4.12	4.80	4.62	3.46	7.30–8.15	3.8	10.5	10.0	10.0	4.2	2.5	12.0
6	5.18	4.95	4.00	3.59	4.00	4.80	4.50	–	7.40–8.10	3.7	10.2	9.0	9.0	4.0	2.4	12.0
8	4.82	4.25	3.98	3.50	3.65	3.75–3.88		–	7.28–7.82	3.6	9.6	9.4	9.2	4.4	2.8	11.0
10	4.40	3.65	5.22	3.68–3.78		4.65–4.72		3.60	7.40–8.18	10.0	9.3	9.5	–	–	–	–
12	5.92			3.55–3.95				–	7.25–8.08	9.8	–	–	–	–	–	–
13	5.97		3.75–3.90			4.50–5.00		–	7.28–8.10	9.8	–	–	–	–	–	–
15	4.35	2.18 1.68	4.55	3.60	3.22	3.85		3.40	7.20–7.88	8.8, 2.2	9.6, 4.3	9.8	9.7	4.3	2.7	12.0
17 + 18[a]	4.66	2.11 1.78	4.70	–	3.62	–	–	3.27	7.30–7.88	–	–	–	–	–	–	–
20	5.85	4.29	5.16	3.99	3.91	–	–	–	7.20–8.08	8.1	10.0	2.3	~1	6.5	–	–
21	6.00	6.04	5.37	4.12	4.00	–	–	–	7.20–8.18	8.3	9.6	3.2	~1	6.4	–	–
23[b]	5.04	5.28	4.38	3.32	3.88	4.10	3.47	2.90	7.00–8.25	3.6	10.0	10.5	10.5	4.6	3.0	12.0
24	4.85	4.37	4.12	3.35– 3.90	4.30	3.35–3.90		3.30	7.30–7.85	3.5	9.8	10.2	10.5	4.5	3.2	12.0
26	4.62	5.18	4.07	3.69	3.55	4.42	3.85	3.50	7.35–8.10	9.5	10.5	10.3	10.4	4.7	3.3	12.0
27[b]	3.98	3.73	5.77	3.57	3.20	4.12	3.48	3.20	7.00–8.10	9.8	10.4	10.3	10.5	4.5	3.4	12.0
29	5.22	5.06	3.80	3.65	4.20	3.92–4.05		–	7.30–8.10	4.0	10.3	10.5	10.4	4.6	3.5	12.0
32[b]	4.09	4.36	5.30	4.14	2.67	4.02	3.37	3.35	7.20–8.30	7.8	10.2	3.8	1.5	1.8	1.8	12.2

[a] Signals for C-5 methyl protons appear at $\delta = 1.18$ and 1.24 with an integral ratio of ~1:1.
[b] Spectrum recorded in C_6D_6.

ation of carbohydrates. In some cases this method allows the direct preparation of partially acylated derivatives (e.g. **3** and **10**), otherwise available only from multistep syntheses. Clear advantages of the applied method are: *in situ* formation of reagents, high yields, mild reaction conditions and simple workup procdures.

Compounds **1, 9** and **19** are commercially available. The sugars **7, 11** and **14** were prepared in the author's laboratory and each of them gave satisfactory analytical and spectroscopic data. Compounds **5**,[12] **16**,[24] **22**,[23] **25**,[23] **28**,[12] **30**,[23] and **31**[23] were synthesized according to literature procedures. Melting points were determined with Kofler and Olympus hot-stage apparatus and are not corrected. Specific optical rotations were measured with a Perkin-Elmer Polarimeter 241. The ^{1}H-NMR spectra were recorded with Bruker SY 200 and Bruker WM 300 instruments. TLC and column chromatography were performed on precoated silica gel plates (Merck 60 F_{245}) and on Kieselgel 60 (Merck 230–400 mesh), respectively, with the following solvent systems: (A) CH_2Cl_2/EtOAc (24:1); (B) hexane/EtOAc (1:1); (C) $CHCl_3$/EtOAc (1:1); (D) toluene/MeOH (85:15); (E) toluene/MeOH (7:3); (F) toluene/MeOH (19:1) (G) CH_2Cl_2; (H) toluene/MeOH (9:1); (I) toluene/EtOAc (4:1); (J) CH_2Cl_2/EtOAc (19:1); (K) CH_2Cl_2/MeOH (99:1). All evaporations were carried out under diminished pressure at ca. 40°C.

Acylation of Carbohydrate Derivatives with In Situ Generated 1-Acyloxy-1*H*-Benzotriazoles; General Procedure:
To a stirred mixture of anhydrous 1-hydroxy-1*H*-benzotriazole (1-HBTZ, 1.1–3.3 mmol) and Et_3N (1.1–3.3 mmol) in dry CH_2Cl_2 (5–15 mL) is added slowly BzCl or TsCl (1.1–3.3 mmol) at r.t. over a period of 20 min. The mixture is stirred for a further 30 min., then a concentrated solution of the sugar (1.0 mmol), to be acylated, in CH_2Cl_2 (5–15 mL) and Et_3N (1.0 mmol) are added in one portion, and stirring is continued for the period indicated in Table 1. The reaction mixture is diluted with CH_2Cl_2 until a clear solution is obtained, and then washed with 10% $NaHCO_3$, water, and dried (Na_2SO_4). After evaporation and co-evaporation with toluene, the residue is purified as indicated in Table 1.

The authors thank the Alexander von Humboldt Foundation (Bonn, Germany) for a research fellowship to I.F.P. This work was supported, in part, by a grant (OTKA 298) from the Hungarian Academy of Sciences and by the Fonds der Chemischen Industrie.

Received: 4 March 1991; revised: 10 June 1991

(1) Alexander von Humboldt research associate at the University of Hamburg. Permanent address: Antibiotic Research Group of the Hungarian Academy of Sciences, P.O.Box 70, H-4010 Debrecen, Hungary.
(2) Sugihara, J.M. *Adv. Carbohydr. Chem.* **1953**, *8*, 1.
(3) Haines, A.H. *Adv. Carbohydr. Chem. Biochem.* **1976**, *33*, 11.
(4) Staab, H.A.; Mannschreck, A. *Chem. Ber.* **1962**, *95*, 1284.
(5) Cicero, D.; Varela, O.; De Lederkremer, R.M. *Tetrahedron* **1990**, *46*, 1131, and references cited therein.
(6) Ueda, M.; Oikawa, H.; Teshrogi, T. *Synthesis* **1983**, *908*, and references cited therein.
(7) Kim, S.; Chang, H.; Kim, W.J. *J. Org. Chem.* **1985**, *50*, 1751.
(8) Williams, J.M.; Richardson, A.C. *Tetrahedron* **1967**, *23*, 1369.
(9) Ogawa, T.; Matsui, M. *Tetrahedron* **1981**, *37*, 2363.
(10) Varela, O.; Cicero, D.; De Lederkremer, R.M. *J. Org. Chem.* **1989**, *54*, 1884.
(11) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon Press, Oxford, 1983.
(12) Pelyvás, I.F.; Lindhorst, Th.K.; Thiem, J. *Liebigs Ann. Chem.* **1990**, *761*.
(13) Holder, N.; Fraser-Reid, B. *Can. J. Chem.* **1973**, *51*, 3357.
(14) Lindhorst, Th.K.; Thiem, J. *Carbohydr. Res.* **1991**, *209*, 119.
(15) Lindhorst, Th.K.; Thiem, J., unpublished results.
(16) Carey, F.A.; Hodgson, K.O. *Carbohydr. Res.* **1970**, *12*, 463.
(17) Hicks, D.R.; Fraser-Reid, B. *Synthesis* **1974**, 203.
(18) Reber, F.; Reichstein, T. *Helv. Chim. Acta* **1945**, *28*, 1164.
(19) Sorkin, E.; Reichstein, T. *Helv. Chim. Acta* **1945**, *28*, 1. Engelhardt, L.M.; Mocerino, M.; Stick, R.V.; White, A.H. *Aust. J. Chem.* **1990**, *43*, 1111.
(20) Ness, R.K.; Fletcher, H.G., Jr.; Hudson, C.S. *J. Am. Chem Soc.* **1959**, *72*, 2200.
(21) Marsh, J.P.; Mosher, C.W.; Acton, E.M.; Goodman, L *J. Chem. Soc., Chem. Commun.* **1967**, 973.
(22) Richtmyer, N.K. *Methods Carbohydr. Chem.* **1962**, *1*, 107.
(23) Carbohydrates (Ed. P.M. Collins), Chapman & Hall, London New York, 1987, # M-00094, p. 347.
(24) Pelyvás, I.; Sztaricskai, F.; Szilágyi, L.; Bognár, R.; Tamás, J *Carbohydr. Res.* **1979**, *68*, 321.