A Novel and Efficient Deprotection of the Allyl Group at the Anomeric Oxygen of Carbohydrates

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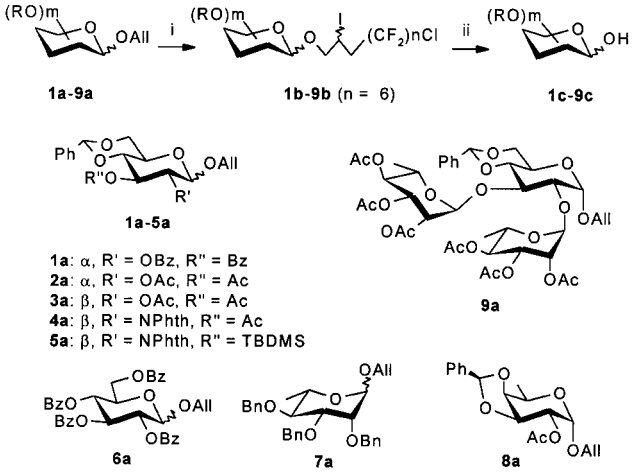
Abstract: Perfluoroalkylation with perfluoroalkyl iodide under sodium dithionite and sodium bicarbonate in acetonitrile/water followed by elimination in the presence of zinc powder and ammonium chloride in ethanol was disclosed to be an extremely mild and efficient procedure for deprotection of the anomeric allyl group of carbohydrates.

Synthetic oligosaccharides and glycoconjugates are indispensable probes for life science and promising drug candidates for the pharmaceutical industry.[1] In the course of synthesizing an oligosaccharide or a glycoconjugate, the manipulation of the anomeric hydroxyl of a carbohydrate plays a pivotal role.[2] The anomeric hydroxyl has to be protected then a carbohydrate can be converted into a glycosylation acceptor; and the anomeric hydroxyl protection has to be released, if it can not directly serve as a leaving group as that in thioglycosides,[3] glycals,[4] 4-pentenyl glycosides,[5] and vinyl glycosides,[6] etc., then a carbohydrate can be used as[7] or functionalized into a variety of glycosyl donors, such as glycosyl imidates,[2b] halides,[2a] and phosphites,[8] etc. Therefore, the protective group for the anomeric hydroxyl not only should stay intact under the conditions for the manipulation of other protective groups and for glycosylation, but also should be selectively removed afterwards without affecting other protective groups. Although, many protective groups have been successfully employed for the anomeric hydroxyl protection in the block synthesis of oligosaccharides and glycoconjugates, such as *tert*-butyldimethylsilyl,[9] 2-trimethylsilylethyl,[10] benzyl,[11] 4-methoxylphenyl,[12] and allyl,[13] etc., there are none generally applicable. Allyl is one of the most commonly used protective group in carbohydrate chemistry,[14] which is compatible with fairly strong acidic or basic conditions, and could be removed under many procedures.[14-18] The most useful conditions for deallylation in carbohydrate chemistry involved the utilization of palladium,[16] rhodium,[17] or iridium species.[18] It seems ideal to use allyl as the protective group for the anomeric hydroxyl of a carbohydrate building block, ignoring the expensiveness of these metal species. However, deblocking the allyl protection at the anomeric hydroxyl of a carbohydrate was found to be very capricious,[16c,19] the results were subtly dependent on the substrates. Herein we disclosed an extremely mild and efficient procedure to remove the anomeric allyl protection. The results are listed in the scheme and table.

Employing the well documented and widely applicable perfluoroalkylation of the terminal carbon carbon double bond with perfluoroalkyl iodide under sodium dithionite/sodium bicarbonate in acetonitrile/water,[22] allyl glycosides (**1a**-**9a**) were perfluoroalkylated under almost neutral conditions at rt. After an easy work up, the anomeric anchor of **1b**-**9b** was eliminated efficiently in the presence of zinc powder and ammonium chloride in ethanol (reflux, 5 min). Both steps were found to be very clean on the TLC, after purification by a silica gel column chromatography, good yields of the corresponding carbohydrates with a free hemiacetal (**1c**-**9c**) were obtained. The most commonly used protective groups, including benzyl, benzoyl, acetyl, benzylidene (either dioxolane-type or dioxane-type), *tert*-butyldimethylsilyl, and N-phthalimide, were all intact. In comparison, some unsuccessful palladium species involving deallylation of the allyl glycosides were listed in the table (entry 10-14).



i) $I(CF_2)_nCl$ (n = 2, 6), $Na_2S_2O_4$, $NaHCO_3$, CH_3CN/H_2O (4/1), rt, 20 min;
ii) Zn, NH_4Cl, EtOH, reflux, 5 min. 50-95% for two steps

Scheme

Table. Deprotection of the allyl group at the anomeric oxygen of carbohydrates (**1a**-**9a**)[a]

Entry	Substrate	Conditions [b]	Yield [%] [c,d]	α/β [e]
1	**1a**	A	95	3.0
2	**2a**		75	1.5
3	**3a**		86	1.1
4	**4a**		82	0.1
5	**5a**		50	0.1
6	**6a**		85	5.0
7	**7a**		73	1.2
8	**8a**		50	1.3
9	**9a**		78	2.8
10	**1a**	B	trace [f]	
11		C	trace [g]	
12		D	trace [h]	
13	**8a**	B	trace [g]	
14		E	trace [g]	

[a]Results by employing $I(CF_2)_6Cl$ in the perfluoroalkylation.[20] [b]Condition A: present procedure;[21] B: $PdCl_2$, NaOAc-HOAc;[16d] C: $PdCl_2$, NaOAc-HOAc-THF; D: Pd/C, MeOH, then HgO, $HgCl_2$;[16g,h] E: $PdCl_2$-CuCl, O_2, DMF/H_2O.[16b] [c]Isolated yield for two steps, not optimized. [d]Both **1b**-**9b** and **1c**-**9c** gave satisfactory analytical data (^1H NMR, ^{19}F NMR, MS). [e]Determined by ^1H NMR. [f]Insoluble. [g]Mainly proceeded Wacker oxidation.[19] [h]The isomerization of the allyl to vinyl was found to be very sluggish

It is worthy noting that the finally removed perfluoroalkane moiety could not only be a ballast but a useful anchor for further purpose, such as for the "fluorous synthesis"[23] of carbohydrates, that is also our current interest.

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20. Herein, $I(CF_2)_nCl$ (n = 2, 6) were gifts from Prof. L. Lü. When perfluoroalkylated with $I(CF_2)_2Cl$, the corresponding products have the same R_f as that of the starting allyl glycosides, therefore the reaction can not be monitored by TLC. Several other perfluoroalkyl iodides are available in Aldrich catalog.
21. Typical procedure: To a stirred solution of **1a** (200 mg, 0.39 mmol) and $I(CF_2)_6Cl$ (180 mg, 1.0equiv) in CH_3CN (12 mL), was added H_2O (3 mL) at rt, the mixture turned to be an emulsion, to which a mixture of $Na_2S_2O_4$ (335 mg, 5.0 equiv) and $NaHCO_3$ (162 mg, 5.0 equiv) was added. After being stirred at rt for 30 min, the mixture was diluted with EtOAc (50 mL), the organic layer separated was washed with brine twice, dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatoghaphed on a silica gel column to give **1b** (96%) or directly treated with Zn powder (125 mg, 5.0 equiv) and NH_4Cl (40 mg, 2.0 equiv) in absolute EtOH, after being refluxed for 5 min, the mixture was cooled to rt, filtered and concentrated. Flash chromatography of the residue on a silica gel column afforded **1c** (85%, based on **1a**). **1b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (m, 4H, Ar), 7.50 (m, 4H, Ar), 7.38 (m, 7H, Ar), 6.20 and 6.14 (2(t, 1H, J = 9.7, H-3'), 5.64 and 5.62 (2 x s, 1H, PhCH), 5.36(m, 1H, H-2'), 4.46-3.70 (m, 8H), 3.05 and 2.75 (2 x m, 2H, H-3) ppm; ^{19}F NMR (TFA as a standard): δ 68.8 (s, 2F, $ClCF_2$), 112.8 (s, 2F, CH_2CF_2), 119.2-121.4 (m, 8F) ppm; EIMS (m/z): 978 (M^+), 930, 830, 696, 506, 105 (100%). **1c**: ^{1}H NMR ($CDCl_3$): δ 8.00 and 7.40 (m, 15H, Ar), 6.13 (t, 0.75H, J = 9.8, H-3α), 5.85 (t, 0.25H, J = 9.7, H-3β), 5.68 (d, 0.75H, J = 3.4, H-1α), 5.56 (s, 0.75H, PhCHα), 5.53 (s, 0.25H, PhCHβ), 5.30 (m, 1.25H, H-2, H-1β), 4.35 (m, 2H), 3.90 (m, 2H) ppm; EIMS (m/z): 476 (M^+), 459, 353, 327, 105 (100%).
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