A Novel, Mild, and Practical Regeneration of Alcohols from their Allylic Ethers by NBS/H_2O

Rafael Robles Diaz,* Concepción Rodríguez Melgarejo, María T. Plaza López-Espinosa, and Isidoro Izquierdo Cubero

Department of Organic Chemistry, University of Granada, 18071 Granada, Spain

Received May 24, 1994

The allyl group is a commonly used protecting group in general organic synthesis and, more specifically, in carbohydrate chemistry[1] for protection of the hydroxyl groups present in these molecules as allyl ethers, due to the easy formation and stability under different reaction conditions of such ethers. From the information available, all reported methods for deallylation involve the isomerization of the allyloxy to a prop-1-enyloxy group followed by either acid hydrolysis or oxidation of the resulting enolether. Isomerization of the allyl to prop-1-enyl group has been classicaly achieved by potassium *tert*-butoxide,[2] but this method only can be used when the substrate does not contain base sensitive functional or protecting groups. Lately, different methods using neutral reaction conditions and transition metal (Rh, Ir, Pd, Pt, Zr, etc.) complex catalysts[3] have been developed, but the high cost of these compounds, partial poisoning of the catalyst, competitive reduction of the allyl to propyl group, as well as other side reactions that may occur during the isomerization process, prompt the search for new deallylation reagents.

It is well known that NBS readily brominates allylic positions under very mild free-radical conditions. Application of this reaction to an allylic ether would be favored by the presence of an atom with a lone electron that might stabilize the intermediate radical,[4] thus affording an α-bromo ether. Hydrolysis of this bromo ether would produce the deprotected hydroxyl group and volatile acrolein (eqs 1 and 2).

$$ROCH_2CH{=}CH_2 + NBS \rightarrow [ROCHCH{=}CH_2] \rightarrow ROCHBrCH{=}CH_2 \quad (1)$$

$$ROCHBrCH{=}CH_2 + H_2O \rightarrow ROH + CH_2{=}CHCHO \quad (2)$$

The following reports on the application of the above method to different carbohydrate derivatives where the allyl group was protecting a primary, secondary, and anomeric hydroxyl group in the presence of other acid and base sensitive protecting groups.

The findings are summarized in Table 1. All compounds, except for 3-*O*-allyl-5,6-di-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**4**) which was prepared for the aim of this work, have been previously reported. Compound **4** was obtained by conventional benzoylation of 3-*O*-allyl-1,2-*O*-isopropylidene-α-D-glucofuranose.[14] The synthesis of 1-*O*-allyl-2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**1**) has been reported[5] but its physical and spectroscopic data were not given, and thus they have been included in this paper.

Treatment of **1**–**5** with NBS in freshly distilled CCl_4[15] under reflux and irradiation caused the formation of the corresponding α-bromo ethers which were subsequently hydrolyzed by aqueous 3 M sodium hydroxide (entries 1 and 2), silica gel (entries 3 and 5), and saturated $NaHCO_3$ solution (entry 4), depending on the other functional groups present in the substrate. Although compounds **3** and **4** both have acyl protecting groups, only **3** suffers partial 5 → 3 acyl migration during the basic hydrolysis (aqueous $NaHCO_3$) of the α-bromo acetal, as could be demonstrated by peracetylation of the resulting mixture to give the corresponding 3,5,6-tri-*O*-acetyl derivative. This acyl migration could be avoided by supporting the reaction mixture on silica gel prior to its column chromatography.

It can be concluded that the method described in this paper is remarkably efficient not only due to its simplicity, economy, and high yield, but also in the high regioselectivity of the bromination, since no byproducts could be detected in the reaction as is usual in other free-radical reactions of sugar derivatives.[4]

Experimental Section

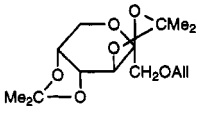
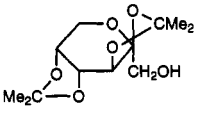
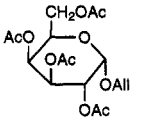
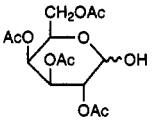
General. All solvents were used dried and freshly distilled. Meltings points were determined with a Gallenkamp apparatus and are uncorrected. Solutions were dried over $MgSO_4$ before concentration under reduced pressure. Optical rotations were measured for solutions in $CHCl_3$ (1-dm tube). TLC was performed on precoated silica gel 60 F_{254} aluminum sheets, using hexane–ether 1:1 as eluent, and detection by charring with H_2SO_4. Column chromatography was performed on silica gel (Merck, 7734) and elution with hexane–ether 2:1.

1-*O*-Allyl-2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (1). To a solution of 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose[6] (2 g, 7.7 mmol) and sodium hydride (0.55 g, 18 mmol) (80% oil dispersion) in anhydrous THF (30 mL) was added allyl bromide (1.3 mL, 15 mmol) and the mixture left at room temperature for 4.5 h. The excess hydride was destroyed by cautious addition of ether saturated with water. The organic phase was separated, washed with water, and concentrated. Column chromatography of the residue yielded **1** (2.17 g, 94%) as a colorless mobile oil: $[\alpha]_D$ −33° (*c*, 1); IR (neat) 3085 (=CH_2); ^{1}H NMR δ 5.86 (ddt, 1H, ^3J_t = 5.4 Hz), 5.25 (dq, 1H, ^4J_q = ^2J_q = 1.7 Hz, ^3J_d = 17.3 Hz), 5.13 (dq, 1H, ^4J_q = ^2J_q = 1.5 Hz, ^3J_d = 10.5 Hz), 4.57 (dd, 1H, $J_{3,4}$ = 2.6 Hz, $J_{4,5}$ = 7.9 Hz), 4.38 (d, 1H), 4.20 (bdd, 1H, $J_{5,6a}$ = 1.9 Hz), 4.10 (ddt, 1H) and 4.01 (ddt, 1H,

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley: New York, 1991. In carbohydrate chemistry: Manthorpe, P. A.; Gigg, R. *Methods Carbohydr. Chem.* **1980**, *8*, 305.
(2) Cunningham, J.; Gigg, R.; Warren, C. D. *Tetrahedron Lett.* **1964**, 1191.
(3) Corey, E. J.; Suggs, W. J. *J. Org. Chem.* **1973**, *38*, 3224. Gent, P. A.; Gigg, R. *J. Chem. Soc., Chem. Commun.* **1974**, 227. Oltvoort, J. J.; van Boeckel, C. A.; de Konig, J. H.; van Boom, J. H. *Synthesis* **1981**, 305. Mereyale, H. B.; Guntha, S. *Tetrahedron Lett.* **1993**, *34*, 6929. Ito, H.; Taguchi, T.; Hanzawa, Y. *J. Org. Chem.* **1993**, *58*, 774.
(4) Somsák, L.; Ferrier, R. J. *Adv. Carbohydr. Chem. Biochem.* **1991**, *49*, 37.
(5) Mitchel, T.; Heesche-Wagner, K. *J. Organomet. Chem.* **1992**, *436*, 43.
(6) Brady, R. F., Jr. *Carbohydr. Res.* **1970**, *15*, 35.
(7) Corbett, W. M.; McKay, J. E. *J. Chem. Soc.* **1961**, 2930.
(8) Schmidt, O. T. *Methods Carbohydr. Chem.* **1963**, *2*, 318.
(9) Gigg, J.; Gigg, R. *J. Chem. Soc. C* **1966**, 82.
(10) Tronchet, J. M. J.; Bourgeois, J. M. *Helv. Chim. Acta* **1971**, *54*, 1580.
(11) Brigl, P.; Grüner, H. *Chem. Ber.* **1933**, 1977.
(12) Helferich, B.; Kashelikar, D. V. *Chem. Ber.* **1957**, *90*, 2094.
(13) Watanabe, K.; Itoh, K.; Araki, Y.; Ishido, Y. *Carbohydr. Res.* **1986**, *154*, 165. Jung, G. L.; Holme, K. R.; Glaudemans, C. P. J.; Lehmann, J.; Lay, H. *Carbohydr. Res.* **1988**, 174, 87.
(14) Nishiyama, S.; Ohgiya, T.; Yamamura, S.; Kato, K.; Takita, T. *Nucleosides Nucleotides* **1992**, *11*, 417.
(15) If freshly distilled CCl_4 was not used partial formation of the acryl ester was observed.

0022-3263/94/1959-7928$04.50/0

Table 1. Deprotection of Allyl Ether by NBS/H_2O

entry	substrate	product[a]	yield[b] (%)	ref[c]
1	 **1**	 **6**	82	5, 6
2	**2**: R = CMe_2; R′ = All	**7**: R = CMe_2; R′ = H	85	7, 8
3	**3**: R = Ac; R′ = All	**8**: R = Ac; R′ = H	78	9, 10
4	**4**: R = Bz; R′ = All	**9**: R = Bz; R′ = H	88	–, 11
5	 **5**	 **10**	quantitative	12, 13

[a] All products were identified by comparison with authentic samples. [b] Isolated product. [c] Reference numbers refer to substrates and products, respectively.

$^2J_{AB}$ = 13.0 Hz), 3.88 (dd, 1H, $J_{6a,6e}$ = 13.0 Hz), 3.70 (d, 1H), 3.56 and 3.52 (two d, 2H, $J_{1,1'}$ = 10.7 Hz), 1.51, 1.44, 1.40, and 1.31 (four s, 12H); ^{13}C NMR δ 134.6, 116.8, 109.0, 108.6, 102.8, 72.8, 71.5, 71.1, 70.3, 70.2, 61.1, 26.6, 25.9, 25.4, and 24.1. MS *m/z* 301 (10.8, $M^+ + 1$), 285 (11.0, $M^+ + 1 - CH_4$), and 243 (100, $M^+ + 1$ – 58 (acetone or allylic alcohol)). Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 60.10; H, 7.83.

3-*O*-Allyl-5,6-di-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose (4). Conventional benzoylation of 3-*O*-allyl-1,2-*O*-isopropylidene-α-D-glucofuranose[14] (2.5 g, 9.6 mmol) with benzoyl chloride (5 mL, 43 mmol) in dry cooled pyridine (25 mL) and then left at room temperature for 24 h gave crystalline **4** (4 g, 90%), after the usual workup and column chromatography: mp 89–90 °C (from ether–hexane); $[\alpha]_D$ –29.4° (*c*, 1); IR (KBr) 1725 (C=O, benzoate); ^{1}H NMR δ 8.04–7.99 and 7.56–7.39 (two m, 10H), 5.98 (d, 1H, $J_{1,2}$ = 3.7 Hz), 5.76–5.64 (m, 2H), 5.15 (dq, 1H, ^4J_q = ^2J_q = 1.5 Hz, ^3J_d = 18.7 Hz), 5.01 (ddd, 1H, ^4J_d = 1 Hz, ^2J_d = 1.5 Hz, ^3J_d = 10.3 Hz), 4.95 (dd, 1H, $J_{5,6}$ = 2.3 Hz, $J_{6,6'}$ = 12.3 Hz), 4.63 (dd, 1H, $J_{3,4}$ = 3.3 Hz, $J_{4,5}$ = 8.5 Hz), 4.59 (d, 1H), 4.57 (dd, 1H, $J_{5,6'}$ = 5.6 Hz), 4.06 (ddt, 1H) and 3.82 (ddt, 1H, $^2J_{AB}$ = 12.3 Hz, low field H: ^3J_d = 5.7 Hz, ^4J_t = 1–1.5 Hz, high field H: ^3J_d = 6.1 Hz), and 3.99 (d, 1H); ^{13}C NMR δ 166.2, 165.3, 133.6, 133.3, 133.0, 130.2, 130.0, 129.8, 128.5, 128.4, 118.4, 112.2, 105.5, 81.1, 81.0, 78.4, 71.5, 69.3, 64.2, 27.0 and 26.4. MS *m/z* 469 (20, $M^+ + 1$), 411 (11, $M^+ + 1$ – 58 (acetone or allylic alcohol)), and 347 (100, $M^+ + 1$ – 122 (benzoic acid)). Anal. Calcd for $C_{26}H_{28}O_8$: C, 66.65; H, 6.02. Found: C, 66.86; H, 5.80.

Deallylation Procedure. To a solution of the allyl ether (**1–5**) (3 mmol) in freshly distilled CCl_4 (100 mL) was added NBS (3 mmol) and the mixture refluxed and irradiated with a Tunsgram Halogen 60000 T8 R7-s-15 lamp in a Pyrex round-bottom flask for 30 min. Reactions were monitored by TLC. The workup of the reaction mixtures was carried out as follows:

Entries 1 and 2. Aqueous 3 M sodium hydroxide solution (100 mL) was added and the mixture stirred for 1 h. The organic phase was separated, washed with water, and concentrated and the residue subjected to column chromatography to yield the corresponding products.

Entries 3 and 5. Silica gel (Merck, 7734, 10 g/g substrate) was added to the reaction mixture and concentrated and the residue chromatographed to afford the related products.

Entry 4. Treatment of the reaction mixture as entries 1 and 2 but with aqueous saturated sodium hydrogen carbonate solution (100 mL) gave **9**.

Supplementary Material Available: Tables of ^{1}H and ^{13}C NMR spectral data for **1–5**, **8** (^{13}C only), and **9** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.