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Carbohydrate Research 342 (2007) 627–630
Carbohydrate RESEARCH

Note

Use of methanesulfonic acid in the reductive ring-opening of *O*-benzylidene acetals

Alexander I. Zinin, Nelly N. Malysheva, Anna M. Shpirt, Vladimir I. Torgov and Leonid O. Kononov*

N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Leninsky prosp., 47, 119991 Moscow, Russian Federation

Received 15 June 2006; received in revised form 6 October 2006; accepted 6 October 2006
Available online 13 October 2006

Dedicated to the memory of Professor Nikolay K. Kochetkov

Abstract—Methanesulfonic acid was shown to be an efficient and convenient substitute for ethereal HCl in reductive 4,6-*O*-benzylidene acetal ring-opening reaction with sodium cyanoborohydride in THF. Normal regioselectivity was observed, the 6-*O*-benzyl ethers with free 4-OH group being the major products of the reaction.

Keywords: Benzylidene acetal; Reduction; Sodium cyanoborohydride; Methanesulfonic acid; Regioselectivity

Chemical synthesis of oligosaccharides currently relies on the use of partially protected mono- and oligosaccharide building blocks. The reductive opening of 4,6-*O*-benzylidene acetals (and other benzylidene acetals with 1,3-dioxane ring) with sodium cyanoborohydride in THF in the presence of HCl in Et_2O (the so-called 'Garegg opening')[1–3] is often used for large-scale preparation of 6-*O*-benzyl derivatives due to a low cost of the reagents. The main drawback of this procedure is associated with the necessity of preparation of soln of HCl in Et_2O by bubbling gaseous HCl (taken from a gas cylinder or generated from NaCl) through cold Et_2O under anhyd conditions. This is a tedious and skill-demanding procedure due to the necessity of ensuring strictly anhyd conditions. Although a soln of HCl in Et_2O is now commercially available, the problem of keeping it anhyd remains relevant. For this reason, other experimentally less demanding approaches became popular. Particularly worthy of note are the Et_3SiH–TFA (Ref. 4), $BH_3\cdot Me_2NH$–$BF_3\cdot OEt_2$ (Ref. 5) and $Me_3N\cdot BH_3$–$AlCl_3$ (Ref. 6) systems. Recently, a more efficient variant of the latter method was described[7] that emphasizes the necessity of performing the reductive opening of benzylidene acetals with $Me_3N\cdot BH_3$ in the presence of water (3:1 $AlCl_3$–water). Obviously, a strong acid is required[3] to effect the reductive opening of benzylidene acetals, hydrogen chloride in diethyl ether being used mainly for historical reasons. We reasoned that another protic acid with an appropriate pK_a value, which is soluble in THF and can be prepared anhyd, would be a possible alternative for ethereal HCl in this reaction. THF is the solvent of choice due to its ability to dissolve a wide range of compounds including salts. Thus, for example, the presence of several amide groups in the molecule of a benzylidene derivative makes the substance so polar that it is usually difficult to use other ether-type solvents such as diethyl ether or 1,4-dioxane for the reaction due to poor substrate solubility in these solvents. The use of THF allows one to minimize the volume of solvent used, a feature very useful on a large scale. A report concerning the use of trifluoromethanesulfonic acid (TfOH) in THF as the proton source in this reaction has been published but no experimental details were provided.[8] The major drawback of TfOH is its extremely high cost.

* Corresponding author. Tel.: +7 495 9383610; fax: +7 495 1355328; e-mail: kononov@ioc.ac.ru

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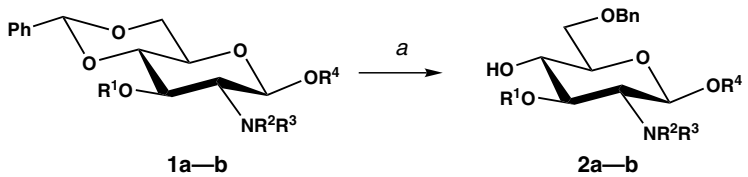
doi:10.1016/j.carres.2006.10.009

In addition, exceptionally high acidity of TfOH may pose problems in some cases. The weaker trifluoroacetic acid does not promote the reductive ring-opening of 4-methoxybenzylidene acetals with $NaBH_3CN$ in DMF,[9] but fails to promote the respective opening of benzylidene acetals. Obviously, another acid, less acidic than TfOH and more acidic than TFA, is required. We assumed that the reasonably cheap methanesulfonic acid (MsOH, pK_a 1.92)[10] could be a good candidate.

Indeed, we have found that MsOH can promote this reaction leading regioselectively to the expected products with free hydroxy group at C-4, which were isolated in high yields. The conditions of the reaction ($NaBH_3CN$, MsOH, MS 4 Å, THF, pH 2–3, ~20 °C) were similar to the traditional ones[3] and can be expected to be compatible with a variety of protective groups (see Scheme 1). Molecular sieves of any type (3 or 4 Å, beads or powder) were successfully used in the reaction promoted by MsOH. As in the Garegg opening, it is important to control the acidity of the medium. The best yields were achieved when the acidity of the reaction mixture was near pH 2.5–3 (measured with a high resolution indicator pH paper (Acilit, E. Merck)). Very low acidity of the reaction medium (pH > 3) does not allow the reaction to proceed, while very high acidity (pH 2 or lower) would lead to the formation of by-products and partial acetal cleavage if traces of moisture were present in the reaction mixture. The actual amount of acid required varies with the amount and type of molecular sieves used. We have also found that although neat MsOH could be added directly to the reaction mixture, in most cases it is more convenient to use a *freshly prepared* 0.5 M soln of MsOH in THF and add it in 1 equiv portions until gas evolution ceases, then add 0.5 equiv more to ensure the correct pH. On a large scale, most of the required MsOH can be added neat, and then a 2 M soln of MsOH in THF is used for fine-tuning the acidity of the reaction medium. Although MsOH does catalyze ring-opening polymerization of THF, this side process does not prevent from using THF as the solvent for the reductive opening of benzylidene acetals. The amount of THF oligomers was especially large when the reaction mixture was left overnight at room temperature. In this case, the THF oligomers are detectable after charring the TLC plate with acid (8:0.7 $CHCl_3$–MeOH, R_f 0.47) and can be separated by silica gel column chromatography (they were identified from the NMR spectra: δ_H 1.50–1.65 (m, 20H, CCH_2C), 3.30–3.50 (m, 21H, CH_2OCH_2, CH_2OH); δ_C 26.4 (9.5C, CCH_2C), 60.8 (1C, CH_2OH), 70.5 (10C, CH_2CH_2-OCH_2)). Therefore, in order to minimize THF polymerization and related side processes, which dramatically decrease the yield of the target product, the reaction should be quenched with a base (Et_3N or aqueous $NaHCO_3$) at least within 1–2 h after complete consumption of the starting benzylidene acetal (at this point the reaction mixture can safely be left overnight at room temperature without affecting the yield of the target product). In fact, this side process does not pose a major problem since in most cases small amounts of THF oligomers could be easily separated from the target 6-*O*-benzyl ethers by chromatography and crystallization. When the reaction is performed on a large scale, the additional advantages of using MsOH rather than ethereal HCl become evident. Thus, the addition of relatively small volumes of MsOH (or its soln in THF) is necessary to effect benzylidene acetal ring opening, while much larger volumes of a soln of HCl in Et_2O are needed to create the required acidity of the medium.

A direct comparison of the two approaches (based on the use of MsOH and HCl) was made using 4-methoxyphenyl glycoside **1a**[11] and 3-(trifluoroacetamido)propyl glycoside **1b**[12] as representative examples. Both reactions were complete within 1–3 h provided the required acidity of the reaction medium was maintained and an excess of $NaBH_3CN$ was present. The isolated yields of 6-*O*-benzyl ethers **2a**,**b** were comparable to those reported.[11,12] In one case, when chromatographic mobility of the desired product **2a** was similar to that of THF oligomers and its direct purification was difficult, the crude reaction mixture was acetylated (Ac_2O/Py) and the product separated from the by-products followed by O-deacetylation to **2a**.

The structures of products **2a**,**b** were inferred from their ^1H and ^{13}C NMR spectra, which were identical to those reported.[11,12] The location of the benzyl group at O-6 in **2a**,**b** was deduced from the low-field position of C-6 ($\delta \sim 70$ ppm—note the incorrect assignment of ^{13}C



1a—b **2a—b**

a: R^1 = Bn, R^2 = R^3 = Pht, R^4 = 4-$MeOC_6H_4$
b: R^1 = Ac, R^2 = H, R^3 = Ac, R^4 = $(CH_2)_3$NHTFA

Scheme 1. Reagents and conditions: (a) $NaBH_3CN$, CH_3SO_3H, MS 4 Å, THF, 20 °C, 1–3 h.

NMR spectrum in Ref. 11 and its absence in Ref. 12) in comparison with that in derivatives with unprotected 6-OH group (δ 60–62 ppm). The ^{1}H NMR spectrum of **2b** contained showed a signal for H-3 at low field (δ_H 5.03 ppm) and a signal for H-4 at high field (δ_H 3.68 ppm), which corroborates the acetylation of O-3 and the absence of acetyl group at O-4.

In conclusion, the suggested procedure for reductive 4,6-*O*-benzylidene acetal ring opening in the presence of $NaBH_3CN$, which makes use of MsOH instead of HCl, is a convenient alternative for the existing methods and is especially useful on a large scale since it avoids the need for preparation of large volumes of ethereal HCl. Due to its experimental simplicity and low cost of reagents, this procedure may find wide applications in academic research and industry.

1. Experimental

1.1. General methods

The reactions were performed in argon atmosphere using commercial reagents (Aldrich and Fluka) and anhyd (where appropriate) solvents purified according to standard procedures. Column chromatography was performed on Silica Gel 60 (40–63 μm, E. Merck). Thin-layer chromatography was carried out on plates with Silica Gel 60 on glass or on aluminum foil (E. Merck). The spots of compounds containing carbohydrates were visualized with 1:10 85% H_3PO_4–96% EtOH with subsequent heating (150 °C). The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 instrument (200.13 and 50.32 MHz, respectively). ^{1}H NMR chemical shifts are referred to the residual signal of $CHCl_3$ (δ_H 7.27); ^{13}C NMR chemical shifts, to the $CDCl_3$ signal (δ_C 77.0). Signal assignments in ^{13}C NMR spectra was based on DEPT-135 experiments. Optical rotation was measured on a JASCO DIP-360 polarimeter at 20–25 °C.

1.2. 4-Methoxyphenyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (2a)

To a mixture of solid 4,6-*O*-benzylidene derivative **1a**[11] (3.25 g, 5.47 mmol) and solid $NaBH_3CN$ (1.38 g, 21.96 mmol) under argon, anhyd THF (80 mL) was added followed by freshly activated powdered molecular sieves 4 Å (4 g). The resulting suspension was stirred (mechanical stirrer) at room temperature for 30 min, and a soln of MsOH (1.42 mL, 21.88 mmol) in THF (10 mL) was then added dropwise within 10 min. The reaction mixture became thick and gas evolution began. After 1 h of vigorous stirring (pH 2.5–3), only a small amount of the starting acetal **1a** remained unreacted (1:4 EtOAc–benzene, R_f 0.74 (**1a**), 0.56 (**2a**)). Additional amounts of $NaBH_3CN$ (0.7 g, 11.14 mmol) and MsOH (0.6 mL, 9.25 mmol) were added (pH 2.5–3) and after 1 h the reaction was complete. Triethylamine (6 mL, 43.17 mmol) and water (8 mL) were added and the reaction mixture was filtered through a Celite pad. The solids were washed with MeOH (100 mL) and the filtrate concentrated. The residue was dissolved in $CHCl_3$ (200 mL), washed with water (3 × 100 mL), dried with Na_2SO_4 and concentrated. The residue (5.4 g) was applied on a silica gel column and eluted with 1:9 → 1:4 EtOAc–hexane to give a fraction (3.59 g), which contained **2a** (1:4 EtOAc–benzene, R_f 0.56; 1:1 EtOAc–hexane, R_f 0.26) contaminated with THF oligomers. This fraction was dissolved in anhyd Py (8 mL) and treated with Ac_2O (8 mL) for 18 h at room temperature. Then MeOH (10 mL) was added and after 1 h the mixture was concentrated. The residue was dissolved in $CHCl_3$ (200 mL), washed with water (2 × 100 mL), dried with Na_2SO_4 and concentrated to a residue which was purified by crystallization from Et_2O–hexanes to give the pure 4-O-acetylated derivative (2.60 g, 75%, 1:4 EtOAc–benzene R_f 0.75, 1:1 EtOAc–hexane R_f 0.56). This material was dried under diminished pressure and dissolved in anhyd THF (45 mL) under argon. To the resulting soln, a 1 N soln of magnesium methoxide in MeOH (45 mL) was added and the mixture was kept at room temperature for 2.5 h. The reaction mixture was neutralized with AcOH and concentrated. The residue was dissolved in $CHCl_3$ (50 mL), concentrated to give the residue (2.42 g), which was redissolved in benzene and purified by silica gel chromatography (1:49 → 1:9 EtOAc–benzene) to give pure compound **2a** (2.24 g, 69%). $[\alpha]_D^{25}$ +56.5 (*c* 1.0, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 55.2 (OMe); 55.5 (C-2); 70.3 (C-6); 73.7 (O*C*H_2Ph); 73.7, 73.9 (C-4, C-5); 74.4 (O*C*H_2Ph); 78.5 (C-3); 97.5 (C-1); 114.3, 118.6, 123.3, 127.4, 127.7, 127.9, 128.1, 128.4, 133.8, (arom. CH); 131.5, 137.6, 138.0, 150.7, 155.3 (arom. C); 167.7 (CO).

1.3. 3-(Trifluoroacetamido)propyl 2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-β-D-glucopyranoside (2b)

To a mixture of solid 4,6-*O*-benzylidene derivative **1b**[12] (6.705 g, 13.29 mmol) and solid $NaBH_3CN$ (7.00 g, 111.39 mmol), anhyd THF (200 mL) was added under argon followed by freshly activated powdered molecular sieves 4 Å (9.6 g). The resulting suspension was magnetically stirred at room temperature for 30 min, and a 2 M soln of MsOH in THF was then added dropwise (using a syringe) at such a rate that the gas evolution was steady and vigorous stirring was possible (the reaction mixture gradually becomes thick). The addition of MsOH soln was continued until pH 2.5–3 was reached (1 h, 80 mL of 2 M MsOH soln was added), and TLC showed the presence of the product in the reaction mixture (8:0.7 $CHCl_3$–MeOH, R_f 0.33 (**1b**), 0.20 (**2b**)) (if the product is not detected at this point, an additional amount of

2 M MsOH soln (5 mL) should be added). Vigorous stirring was continued at room temperature (20–25 °C), and after 3 h no starting material was present in the reaction mixture (if the reaction was incomplete, more $NaBH_3CN$ (1 equiv, 1.00 g, 13.23 mmol) should be added accompanied by the amount of MsOH soln necessary to attain pH 2.5–3). The reaction mixture was cooled in an ice water bath and satd aq $NaHCO_3$ (100 mL) was added (at this point the reaction mixture can be left overnight at room temperature without affecting the yield of the target product **2b**) and the solids were filtered off. The filtrate was extracted with $CHCl_3$ (3×120 mL), the organic extract was washed with satd aq $NaHCO_3$ (3×50 mL), dried by filtration through 1:1 mixture Na_2SO_4–Celite (solids were washed with $CHCl_3$) and the filtrate was concentrated to give a foam (7.3 g), which was dissolved in $CHCl_3$ (35 mL) and AcOEt (4 mL) and applied on a silica gel column and then eluted with $CHCl_3$–MeOH mixtures (gradient 0→10% MeOH) to give pure **2b** as a white foam (6.128 g, 91%). Crystallization from AcOEt–Et_2O–hexanes afforded 3.12 g (46%) of **2b** as white crystals, mp 132–133 °C, $[\alpha]_D^{22}$ −70.4 (*c* 1.0, $CHCl_3$), lit.[12] $[\alpha]_{546}^{25}$ −93 (*c* 0.6, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 20.9 (CH_3CO_2); 23.1 (CH_3CON); 28.4 ($CH_2CH_2CH_2$); 37.2 (CH_2N); 53.8 (C-2); 66.7 (OCH_2CH_2); 69.9 (C-6); 70.2 (C-4); 73.6 (OCH_2Ph); 74.3 (C-5); 75.4 (C-3); 101.2 (C-1); 127.7, 127.9, 128.4 (Ph); 137.5 (arom. C); 171.0, 172.0 (CO). Anal. Calcd for $C_{22}H_{29}F_3N_2O_8$: C, 52.15; H, 5.77; N, 5.53. Found: C, 51.97; H, 5.82; N, 5.62.

Acknowledgement

This work was supported by the Russian Foundation for Basic Research (Project No. 06-03-33035).

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