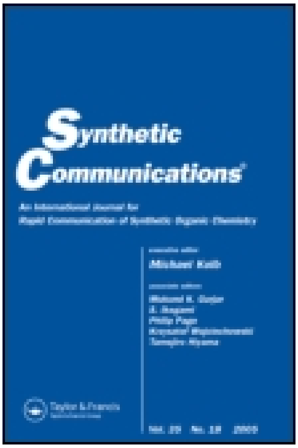

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Microwave-Assisted Rapid Deacetalation of Carbohydrates

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Abstract: A simple and fast procedure to deprotect carbohydrate 4,6-di-*O*-benzylidene acetals was accomplished by using domestic microwave-oven irradiation in solvent-free conditions and with silica-gel-supported reagents.

Keywords: Deacetalation, microwave, solvent-free

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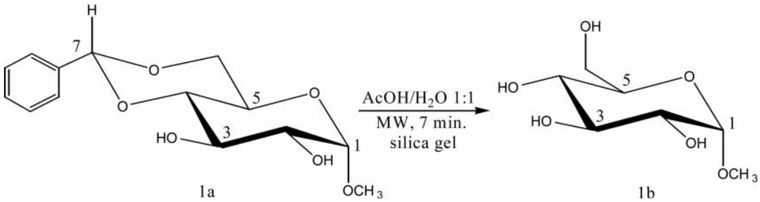
Protective groups play an important role in organic synthesis, mainly in the field of carbohydrate chemistry. Carbohydrate hydroxyl groups are usually protected by conversion into acetals, esters, and ethers. Efficient selective protection–deprotection is required for the appropriate manipulation of hydroxyl groups in synthesis procedures.[1] Because faster and simpler methods are always needed in organic synthesis, since 1986 microwave irradiation has been increasingly used as a laboratory method to accelerate synthetic transformations[2] in a clean, effective, and convenient way. Additionally, heating reactants often results in higher yields and shorter reaction times.[3]

Reactions under "dry conditions" (in the absence of a solvent on solid support with or without catalysts) were originally developed in the late 1980s.[4] Microwave heating has been proven to be of benefit, in particular for reactions without solvents, which are often expensive, toxic, and difficult to remove, specifically solvents with high boiling points.[4] Moreover, the absence of solvent reduces explosion hazards in microwave-oven reactions. During microwave-induced reactions under "dry conditions," the reactants are adsorbed onto the surface of alumina, silica gel, clay, and other supports. Consequently, supported reagents afford safe and simple reaction conditions and an opportunity to work with open vessels in domestic microwave-oven rather than in expensive laboratory microwave systems. Some papers on protecting-group chemistry have been published, but most of them involve solvent-free techniques of deprotection of different protecting groups.[5] We herein describe a method for fast deacetalation of carbohydrates assisted by domestic microwave-oven heating and using silica gel as a solid support with good yield.

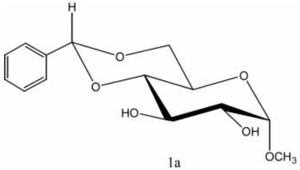
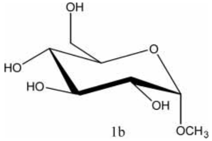
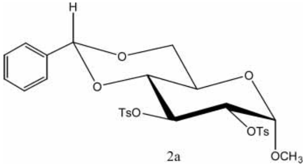
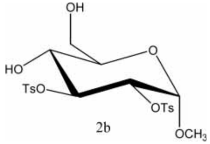
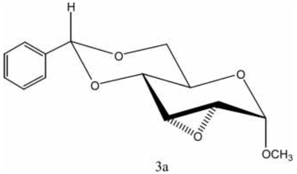
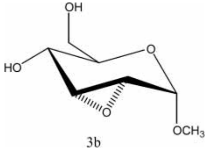
The reactions were carried out by simply mixing 4,6-di-*O*-benzylidene acetals with $H_2O/AcOH$ 1 : 1 (Scheme 1). The mixtures were adsorbed onto silica gel and then heated in a domestic microwave oven in an open vessel for 7 min. The results are summarized in Table 1. Deacetalation of the carbohydrate shown in entry 2 (Table 1) with microwave heating in these conditions was also tried, but it did not afford the deprotected product in a good yield in a short reaction time. Thus, the deacetalation product was obtained by reaction without support with a yield of 71%, as described in Table 1.

The workup procedure is reduced to the treatment with an appropriate solvent (e.g., methyl alcohol or acetone), simple filtration, solvent



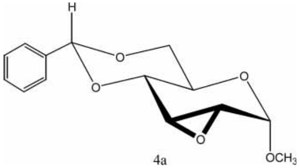
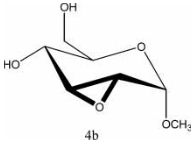
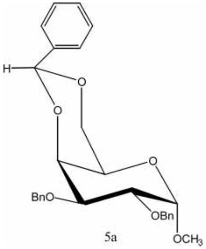
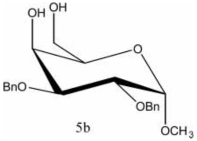
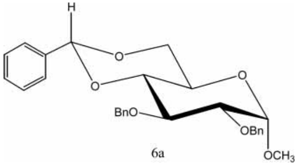
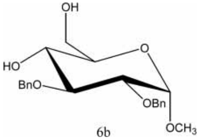
Scheme 1.

Table 1. Deacetalation of carbohydrates under microwave irradiation

Entry	Acetal carbohydrates	Products	AcOH/H_2O 1 : 1 (mL)	Carbohydrate/SiO_2 (mmol : g)	Yield (%)
1	 1a	 1b	4.50	0.355/2.0	93
2	 2a	 2b	0.56	0.042/[a]	71
3	 3a	 3b	1.44	0.114/1.0	81

(*continued*)

Table 1. Continued

Entry	Acetal carbohydrates	Products	AcOH/H_2O 1 : 1 (mL)	Carbohydrate/SiO_2 (mmol : g)	Yield (%)
4	 4a	 4b	9.56	0.757/2.0	90
5	 5a	 5b	2.72	0.216/2.0	83
6	 6a	 6b	2.72	0.216/2.0	81

[a] Without support.

evaporation, and the removal of excess acetic acid and water under reduced pressure. The products were obtained with good yields and purity for use in the subsequent reactions. All products were confirmed by ^{1}H NMR.

To the best of our knowledge, there is only one example of debenzylidenation of carbohydrates using microwave-oven irradiation in the literature.[2,5] It describes the deacetalation of methyl 4,6-*O*-benzilidene-α-D-glucopyranoside with an 89% yield using MeOH/H_2O at 150°C for 2 min. Heating was performed with a laboratory microwave system and the reaction was carried out in a closed vessel. In the method reported here, deacetalation of six carbohydrates was accomplished by using a domestic microwave oven as an irradiation source and an open vessel. Benzylidene removal was also achieved with high yields and short time. It should also be noticed that the deprotection reaction condition used in the present work was efficiently selective. Although the carbohydrates used presented different substituting groups, no secondary products were formed in any case.

In conclusion, we have developed a simple carbohydrate deacetalation method in the absence of any organic solvent. This procedure furnished "one-spot" TLC reactions with satisfactory yields and purity. Furthermore, heating with domestic microwave-oven irradiation has led to faster deprotection than conventional heating.[6,7]

EXPERIMENTAL

^{1}H NMR spectra were recorded using a BRUKER AVANCE DRX/400 in $CDCl_3$, CD_3SO, or D_2O with TMS as an internal standard. Melting points were determined on a Mettler FP80HT apparatus and are uncorrected. Microwave irradiation was carried out with a domestic microwave oven, General Electric JEI 1145 AWA, at 2450 MHz.

General Carbohydrate Deacetalation Procedure

A mixture of carbohydrate and H_2O/AcOH 1 : 1 (1 mmol/12.5 mL) adsorbed onto silica gel (Table 1) was heated in a domestic microwave oven in an open flask for 7 min. Subsequently, the reaction mixture was washed while stirred with either methyl alcohol or acetone depending on the carbohydrate, and silicagel was removed by filtration. Finally, the solvent and excess H_2O/AcOH were evaporated under reduced pressure to afford the deprotection product.

Compound (1b), methyl α-D-glucopyranoside. Mp: 165–166°C (lit.[8] 169°C); ^{1}H NMR (D_2O, 400 MHz): δ 4.76 (1H, d, H-1, $J_{1,2} = 3.6$ Hz), 3.82 (1H, dd, H-6a, $J_{6a,5} = 1.6$ Hz, $J_{6a,6b} = 12.3$ Hz), 3.70 (1H, dd, H-6b, $J_{6b,5} = 5.4$ Hz, $J_{6a,6b} = 12.3$ Hz), 3.60 (2H, m, H-3 and H-5), 3.51 (1H, dd, H-2, $J_{2,3} = 9.7$ Hz), 3.71 (3H, s, $OC\underline{H}_3$), 3.32 (1H, t, H-4, $J_{3,4} = J_{4,5} = 9.7$ Hz).

Compound (2b), methyl 2,3-di-*p*-toluenesulphonyl-*α*-D-glucopyranoside. (This compound could not be crystallized).[9] ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.76; 7.04 (2H, d, $J_{2',3'} = 8.2$ Hz; -OTs); 7.65; 7.32 (2H, d, $J_{3',4'} = 8.2$ Hz; -OTs); 4.89 (1H, t, H-3, $J_{3,4} = 9.2$ Hz); 4.77 (1H, d, $J_{1,2} = 3.4$ Hz); 4.31 (1H, dd, H-2, $J_{2,3} = 9.2$ Hz); 3.91–3.78 (1H, m, H-5); 3.76 (1H, t, H-6b, $J_{6b-6a} = 9.2$ Hz); 3.64 (1H, t, H-6a, $J_{6a-6b} = 9.2$ Hz); 3.41 (1H, t, H-4); 3.26 (3H, s, $OC\underline{H}_3$); 2.44 (3H, s, $\underline{H}_3C$-Ph); 2.43 (3H, s, $\underline{H}_3C$-Ph).

Compound (3b), methyl 2,3-anhydro-*α*-D-allopyranoside. Mp: 98–100°C (lit.[10] 103–105°C); ^{1}H NMR (CD$_3$SO, 400 MHz): δ 5.20 (1H, d, -CHO$\underline{H}$, $J_{O\underline{H},H\text{-}4} = 6.5$ Hz); 4.85 (1H, d, H-1, $J_{1,2} = 3.0$ Hz); 4.55 (1H, t, –CH$_2$O$\underline{H}$, $J_{O\underline{H},\ H\text{-}6} = 5.7$ Hz); 3.70–3.49 (2H, m, H-4, H-6a); 3.50–3.40 (4H, m, H-2, H-3, H-5, H-6b); 3.35 (3H, s, $OC\underline{H}_3$).

Compound (4b), methyl 2,3-anhydro-*α*-D-mannopyranoside. Mp: 83–84°C (lit.[11,12] 81–82°C) ^{1}H NMR (CD$_3$SO, 400 MHz): δ 5.20 (1H, d, CHO$\underline{H}$, $J_{O\underline{H},H\text{-}4} = 6.0$ Hz); 4.77 (1H, broad singlet, H-1); 4.62 (1H, t, CH$_2$O$\underline{H}$, $J_{O\underline{H},\ H\text{-}6} = 6.0$ Hz); 3.46–3.32(2H, m, H-3, H-5), 3.46–3.38 (5H, m, H-3, H-4, H-5, H-6a, H-6b); 3.41 (3H, s, $OC\underline{H}_3$); 3.26 (1H, d, H-2, $J_{2,3} = 3.7$ Hz).

Compound (5b), methyl 2,3-di-*O*-benzyl-*α*-D-galactopyranoside. Mp: 81–83°C (lit.[13] 83–86°C); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.41–7.24 (10H, m, 2 × $C_6\underline{H}_5$); 4.80 (2H, d, 2 × PhC$\underline{H}$, $J = 11.8$ Hz); 4.67 (3H, m, 2 × PhC$\underline{H}$,H-1); 4.03–3.74 (6H, m, H-2, H-3, H-4, H-5, H-6a and H-6b); 3.36 (3H, s, $OC\underline{H}_3$).

Compound (6b), methyl 2,3-di-*O*-benzyl-*α*-D-glucopyranoside. Mp: 78–79°C (lit.[1] 75–76°C); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.36–7.24 (10H, m, 2 × $C_6\underline{H}_5$); 4.99 (1H, d, PhC$\underline{H}$, $J = 11.5$ Hz); 4.73 (1H, d, PhC$\underline{H}$, $J = 12$ Hz); 4.71 (1H, d, PhC$\underline{H}$, $J = 11.5$ Hz); 4.63 (1H, d, PhC$\underline{H}$, $J = 12$ Hz); 4.59 (1H, d, H-1, $J_{1,2} = 3.5$ Hz); 3.80–3.73 (3H, m, H-2, H-3, H-4); 3.60-3.46 (3H, m, H-5, H-6a and H-6b), 3.35 (3H, s, $OC\underline{H}_3$).

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