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Tetrahedron Letters 47 (2006) 4337–4341
Tetrahedron Letters

Sulfuric acid immobilized on silica: an efficient promoter for one-pot acetalation–acetylation of sugar derivatives☆

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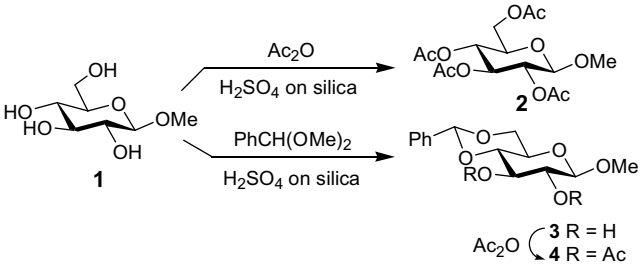
Received 26 January 2006; revised 18 April 2006; accepted 26 April 2006

Dedicated to my mentor Professor Nirmolendu Roy

Abstract—Sulfuric acid immobilized on silica gel has been used as an efficient and safe alternative promoter for acetalation and subsequent acetylation of sugar glycosides using stoichiometric reagents without work-up. The synthesis of different types of per-*O*-acetylated acetals/ketals has been achieved from various types of *O*- and *S*-glycosides in excellent yields.

The use of stoichiometric reagents and catalytic promoters to minimize waste has become a demanding challenge for synthetic chemists when atom economy and green chemistry are considered.[1] Various attempts have been made to achieve this goal by using efficient promoters and so minimizing work-ups.[2] Selective protection of 1,2-*cis*-diols through the formation of acetal or ketal derivatives is a routine reaction in carbohydrate chemistry.[3] Usually these reactions are carried out with an aldehyde or ketone in the presence of a Lewis acid promoter.[4] For more efficient reactions, the use of dimethyl acetals,[5] ketals[6] or enol–ethers[7] are also well known in the literature. Commonly used catalysts for these reactions include formic acid,[8] $CuSO_4$,[9] $ZnCl_2$,[10] *p*-toluenesulfonic acid,[11] camphorsulfonic acid[12] and iodine.[13] Acetalation under basic conditions using dibromotoluene in the presence of pyridine[14] has also been used. However, most of these systems require a large excess of the reagents and therefore, extensive work-up, and chromatographic purification becomes inevitable. So there is a clear need for a practical synthetic strategy that will provide access to these important sugar building blocks using stoichiometric reagents. It is worth noting that recently the use of perchloric acid immobilized on silica has been reported to provide access to per-*O*-acetylated sugar acetals or ketals in excellent yields under stoichiometric conditions.[15] However, perchloric acid is known to be potentially explosive; therefore, safety concerns limit the use of this reagent for large-scale preparations. Recent reports on the utilization of H_2SO_4–silica in various organic reactions,[16] including the acetylation of aliphatic and aromatic alcohols,[17] prompted us to investigate its use as an alternative promoter to synthesize these important sugar building blocks. This letter describes a one-pot reaction using H_2SO_4 immobilized on silica[18] that provides access to per-*O*-acetylated sugar acetals or ketals from unprotected sugar glycosides.

Treatment of methyl-β-D-glucopyranoside (**1**) with stoichiometric acetic anhydride and H_2SO_4–silica led to the per-*O*-acetylated derivative **2** in an excellent yield (Scheme 1). Free reducing sugars also underwent per-*O*-acetylation in good to excellent yields. When methyl-β-D-glucopyranoside (**1**) was treated with 1 mol equiv of benzaldehyde dimethylacetal, in the presence



Scheme 1.

☆ CDRI Communication No. 6923.

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doi:10.1016/j.tetlet.2006.04.118

of H_2SO_4–silica in dry acetonitrile,[19] the corresponding 4,6-*O*-benzylidene acetal (**3**) was formed within 25 min (TLC). The compound collected after filtration proved to be pure by NMR and mass spectrometry. After complete conversion to the benzylidene derivative, as judged by TLC, 4 mol equiv of acetic anhydride were added and the mixture stirred for 30 min at room temperature. Filtration and evaporation of the solvents resulted in methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**4**) in 93% yield. The formation of 2 mol equiv of methanol, during the benzylidene reaction using 1 mol equiv of benzaldehyde dimethylacetal, justified the necessity of 4 mol equiv of acetic anhydride for acetylation. The compatibility of H_2SO_4–silica with the relatively less robust *cis*-decalin system was confirmed when *p*-methoxyphenyl β-D-galactopyranoside (**5**) gave *p*-methoxyphenyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-galactopyranoside (**6**) in 89% yield. This example also confirmed that H_2SO_4–silica is compatible with the relatively acid labile *p*-methoxyphenyl glycosides. Other *O*-glycosides, for example, *n*-octyl, trimethylsilyl, and thioglycosides, also gave satisfactory results under these conditions (Table 1). The applicability of this reagent system was further extended with the formation of per-*O*-acetylated 4-methoxylbenzylidene, 4-nitrobenzylidene, and 3-chlorobenzylidene derivatives using 4-methoxy, 4-nitro, and 3-chlorobenzaldehydes, respectively[20] (Table 1 entries 5, 6, and 7).

After the successful execution of the one-pot strategy for making per-*O*-acetylated benzylidene acetals, the applicability of the reagent system was assessed for isopropylidene ketals. Treatment of a mixture of methyl α-L-rhamnopyranoside (**17**) in dry acetonitrile with 1 mol equiv of 2,2-dimethoxypropane in the presence of H_2SO_4–silica afforded the corresponding isopropylidene ketal in >95% purity, as confirmed by ^1H NMR and mass spectrometry after filtration and evaporation of the solvents. A sequential acetylation reaction was also performed successfully in the same pot using 3 mol

Table 1. H_2SO_4–silica promoted one-pot benzylidenation/isopropylidenation–acetylation of different glycosides

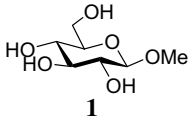
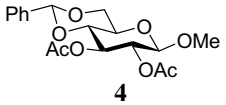
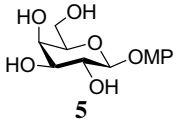
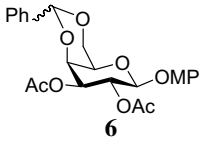
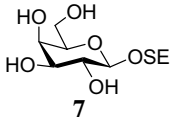
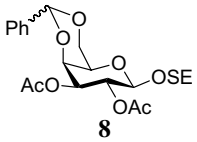
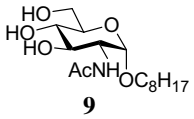
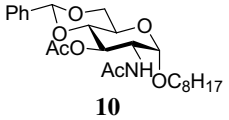
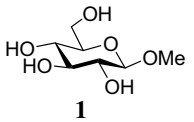
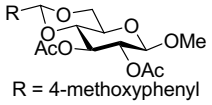
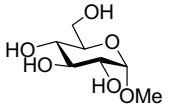
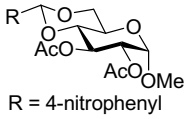
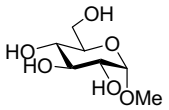
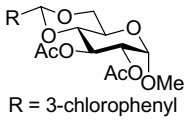
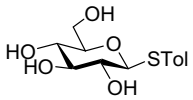
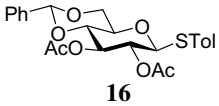
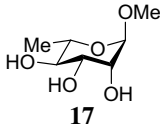
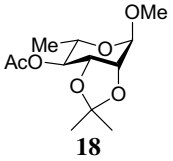
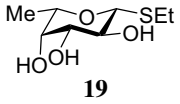
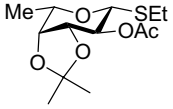
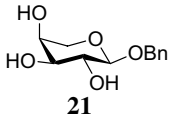
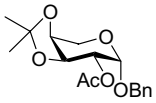
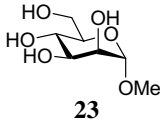
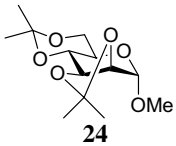
Entry	Starting material	Product	Time[a] (min)	Yield (%)	Ref.
1	 **1**	 **4**	60	93	22
2	 **5**	 **6**	60	89	23
3	 **7**	 **8**	60	90	24
4	 **9**	 **10**	60	82	25
5	 **1**	 R = 4-methoxyphenyl **11**	60	87	26
6	 **12**	 R = 4-nitrophenyl **13**	90	75	27
7	 **12**	 R = 3-chlorophenyl **14**	90	78	28

Table 1 (*continued*)

Entry	Starting material	Product	Time[a] (min)	Yield (%)	Ref.
8	 **15**	 **16**	60	88	29
9	 **17**	 **18**	45	95	30
10	 **19**	 **20**	45	93	31
11	 **21**	 **22**	30	91	15
12	 **23**	 **24**	45	92	32

MP: 4-methoxyphenyl and SE: 2-trimethylsilylethyl.

[a] Total time required for acetalation/ketalation and acetylation.

equiv of acetic anhydride to give methyl 4-*O*-acetyl-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**18**) in 95% yield.[21] Similarly other *O*-glycosides, such as benzyl and thioglycosides also led to the desired products in excellent yield (Table 1). It is worth noting that methyl α-D-mannopyranoside (**23**) gave only 2,3;4,6-di-*O*-isopropylidene ketal (**24**) when treated with 2 mol equiv of 2,2-dimethoxypropane under the same conditions. The use of 1 mol equiv of 2,2-dimethoxypropane led to an incomplete conversion of the starting material.

A 25 mmol scale benzylidenation–acetylation reaction with methyl-β-D-glucopyranoside (**1**) using stoichiometric reagents gave the desired product without affecting the overall yield, which suggested that the reagent system is equally viable on a large scale. After filtration of the product, the H_2SO_4–silica was recovered and used again after drying. Five recycles showed almost no change in the reactivity or the yield of the desired product.

In conclusion, a sequential one-pot strategy for making per-*O*-acetylated benzylidene acetals or isopropylidene ketals of *O*- and *S*-glycosides under stoichiometric conditions has been developed using safe and easy to handle H_2SO_4–silica. This strategy is compatible with various glycosides, including acid labile *p*-methoxyphenyl glycosides, and is equally applicable to large-scale synthesis.

Acknowledgements

Instrumentation facilities from SAIF, CDRI are gratefully acknowledged. I thank Dr. Raja Roy for useful discussions during the course of this work, and Mr. Abhijeet Deb Roy for assistance with acquiring NMR spectra.

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18. *Preparation of H_2SO_4 immobilized on silica:* To a slurry of silica gel (5 g, mesh 60–120, Spectrochem, India) in diethyl ether (20 mL) was added commercially available concd H_2SO_4 (250 μL), and the solvents were evaporated under vacuum. The free flowing silica thus obtained was heated at 110 °C for 2 h and kept in a desiccator over P_2O_5 for further use.
19. *General procedure for benzylidenation–acetylation:* To a mixture of sugar glycoside (1 mmol) in dry acetonitrile (5 mL), benzaldehyde dimethylacetal (1 mmol) was added, followed by H_2SO_4–silica (50 mg). The mixture was stirred at room temperature until TLC revealed complete conversion of the starting material to a faster moving component. Acetic anhydride (4 mmol) was added and stirring continued until TLC showed complete conversion to the diacetates. Filtration through a pad of Celite® and evaporation of the solvent under vacuum yielded the desired products in >95% purity, as judged by ^{1}H NMR.
20. For the synthesis of compounds **10**, **11**, and **13**, 4-methoxybenzaldehyde, 3-chlorobenzaldehyde, and 4-nitrobenzaldehyde were used instead of benzaldehyde dimethylacetal. The remainder of the procedure was the same as before.
21. *General procedure for isopropylidenation–acetylation:* To a mixture of sugar glycoside (1 mmol) in dry acetonitrile (5 mL), 2,2-dimethoxypropane (1 mmol) was added, followed by H_2SO_4–silica (50 mg). The mixture was stirred at room temperature until TLC revealed complete conversion of the starting material to a faster moving component. Acetic anhydride (3 mmol) was added and stirring continued until TLC showed complete conversion to the acetates. Filtration through a pad of celite® and evaporation of the solvent under vacuum yielded the desired products in >95% purity, as judged by ^{1}H NMR. For the mannose derivative (**23**), 2 mmol of 2,2-dimethoxypropane was added and the di-isopropylidene derivative (**24**) was isolated by filtration and evaporation of the solvents.
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23. *4-Methoxyphenyl 2,3-di-O-acetyl-4,6-O-benzylidene-β-D-galactopyranoside* (**6**). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51–6.76 (m, 9 H, ArH); 5.57 (dd, 1H, $J_{1,2} = 8.1$ Hz, $J_{2,3} = 10.2$ Hz, H-2); 5.45 (s, 1H, C*H*Ph); 5.04 (dd, 1H, $J_{2,3}$, $J_{3,4} = 3.3$ Hz, H-3); 4.89 (d, 1H, $J_{1,2} = 8.1$ Hz, H-1); 4.35 (d, 1H, $J_{3,4} = 3.3$ Hz, H-4); 4.29, 4.20 (2bd, 2H, $J_{6a,6b} = 12.3$ Hz, H-6a, H-6b); 3.71 (s, 3H, $C_6H_4OCH_3$), 3.53 (m, 1H, H-5); 2.09, 2.05 (2s, 6H, $2 \times COCH_3$). ESI MS *m*/*z* 481.1 [M+Na].
24. *2-Trimethylsilylethyl 2,3-di-O-acetyl-4,6-O-benzylidene-β-D-galactopyranoside* (**8**). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65–7.39 (m, 5H, ArH); 5.55 (s, 1H, C*H*Ph); 5.15 (dd, 1H, $J_{1,2} = 7.8$ Hz, $J_{2,3} = 10.2$ Hz, H-2); 5.04 (dd, 1H, $J_{2,3}$, $J_{3,4} = 3.6$ Hz, H-3); 4.45 (d, 1H, $J_{1,2} = 7.8$ Hz, H-1); 4.00 [m, 1H, O–C*H*$_2$–CH$_2$–Si(CH$_3$)$_3$]; 3.78–3.53 (m, 3H, H-5, H-6a, H-6b); 3.50 [m, 2H, O–C*H*$_2$–CH$_2$–Si(CH$_3$)$_3$]; 2.03, 2.00 (2s, 6H, $2 \times COCH_3$); 0.89 [m, 2H, O–CH$_2$–C*H*$_2$–Si(CH$_3$)$_3$]; 0.02 [s, 9H, O–CH$_2$–CH$_2$–Si(C*H*$_3$)$_3$]. ESI MS *m*/*z* 475.1 [M+Na].
25. *n-Octyl 2-acetamido-3-O-acetyl-2-deoxy-4,6-O-benzylidene-α-D-glucopyranoside* (**10**). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44–7.31 (m, 5H, Ar.H); 5.86 (d, 1H, $J_{2,NH} = 9.6$ Hz, N*H*); 5.50 (s, 1H, C*H*Ph); 5.29 (t, 1H, $J_{2,3} = J_{3,4} = 9.6$ Hz, H-3); 4.79 (d, 1H, $J_{1,2} = 3.2$ Hz, H-1); 4.34 (dt, 1H, $J_{2,3}$, $J_{3,4}$, $J_{2,NH} = 9.6$ Hz, H-2); 4.26 (dd, 1H, $J_{5,6} = 4.8$ Hz, $J_{6a,6b} = 10.4$ Hz, H-6a); 3.88 (m, 1H, H-5); 3.79 (t, 1H, $J_{3,4} = J_{4,5} = 9.6$ Hz, H-4); 3.68 (m, 2H, H-6b, OC*H*$_2$); 3.38 (m, 1H, OC*H*$_2$); 2.03 (s, 3H, COC*H*$_3$); 1.92 (s, 3H, NHCOC*H*$_3$); 1.58 (m, 2H, OCH$_2$C*H*$_2$); 1.29 (m, 10H, $5 \times$ octyl CH$_2$); 0.87 (t, 3H, $J = 5.7$ Hz, octyl–C*H*$_3$). ESI MS *m*/*z* 486.3 [M+Na].
26. *Methyl 2,3-di-O-acetyl-4,6-O-(4-methoxybenzylidene)-β-D-glucopyranoside* (**11**). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35, 6.87 (2d, 4H, $J = 6.9$ Hz, ArH); 5.46 (s, 1H, C*H*Ph); 5.30 (t, 1H, $J_{2,3} = J_{3,4} = 9.3$ Hz, H-3); 4.95 (dd, 1H, $J_{1,2} = 7.8$ Hz, $J_{2,3}$, H-2); 4.50 (d, 1H, $J_{1,2}$, H-1); 4.36 (dd, 1H, $J_{5,6} = 4.8$ Hz, $J_{6a,6b} = 10.5$ Hz, H-6a); 3.80 (s, 3H, $C_6H_4OCH_3$); 3.75 (m, 1H, H-6b); 3.68 (t, 1H, $J_{3,4} = J_{4,5} = 9.3$ Hz, H-4); 3.51 (s, 3H, OC*H*$_3$); 3.47 (m, 1H, H-5); 2.06, 2.03 (2s, 6H, $2 \times COCH_3$). ESI MS *m*/*z* 419.2 [M+Na].
27. *Methyl 2,3-di-O-acetyl-4,6-O-(4-nitrobenzylidene)-α-D-glucopyranoside* (**13**). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.12, 7.56 (2d, 4H, $J = 7.0$ Hz, ArH); 5.54 (s, 1H, C*H*Ph); 5.49 (t, 1H, $J_{2,3} = J_{3,4} = 9.6$ Hz, H-3); 4.90 (d, 1H, $J_{1,2} = 5.1$ Hz, H-1); 4.84 (dd, 1H, $J_{1,2} = 5.1$ Hz, $J_{2,3} = 9.6$ Hz, H-2); 4.27 (dd, 1H, $J_{5,6} = 4.5$ Hz, $J_{6a,6b} = 9.6$ Hz, H-6a); 3.90 (m, 1H, H-5); 3.75 (t, 1H, $J_{6a,6b} = 9.6$ Hz, H-6b); 3.63 (t, 1H, $J_{3,4} = J_{4,5} = 9.6$ Hz, H-4); 3.36 (s, 3H, OC*H*$_3$); 2.04, 2.02 (2s, 6H, $2 \times COCH_3$). ESI MS *m*/*z* 434.1 [M+Na].
28. *Methyl 2,3-di-O-acetyl-4,6-O-(3-chlorobenzylidene)-α-D-glucopyranoside* (**14**). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42–7.23 (m, 4H, ArH); 5.56 (t, 1H, $J_{2,3} = J_{3,4} = 9.6$ Hz, H-3); 5.45 (s, 1H, C*H*Ph); 4.92 (d, 1H, $J_{1,2} = 3.6$ Hz, H-1); 4.90 (dd, 1H, $J_{1,2} = 3.6$ Hz, $J_{2,3} = 9.6$ Hz, H-2); 4.30–4.28 (m, 1H), 4.27 (dd, 1H, $J_{5,6} = 4.8$ Hz, $J_{6a,6b} = 10.2$ Hz, H-6a); 3.91 (m, 1H, H-5); 3.74 (t, 1H, $J_{6a,6b} = 10.2$ Hz, H-6b); 3.62 (t, 1H, $J_{3,4} = J_{4,5} = 9.6$ Hz, H-4); 3.39 (s, 3H, OC*H*$_3$); 2.07, 2.04 (2s, 6H, $2 \times COCH_3$). ESI MS *m*/*z* 423.1 [M+Na].
29. *p-Tolyl 2,3-di-O-acetyl-4,6-O-benzylidene-1-thio-β-D-glucopyranoside* (**16**). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45–7.14 (m, 9H, ArH); 5.48 (s, 1H, C*H*Ph); 5.33 (t, 1H, $J_{2,3} = J_{3,4} = 9.2$ Hz, H-3); 4.98 (t, 1H, $J_{1,2} = 9.2$ Hz, $J_{2,3}$, H-2); 4.74 (d, 1H, $J_{1,2} = 9.2$ Hz, H-1); 4.37 (dd, 1H, $J_{5,6} = 4.4$ Hz, $J_{6a,6b} = 10.2$ Hz, H-6a); 3.78 (t, 1H, $J_{3,4} = J_{4,5} = 9.2$ Hz, H-4); 3.64 (t, 1H, $J_{6a,6b} = 10.2$ Hz, H-6b); 3.53 (m, 1H, H-5); 2.36 (s, 3H, $SC_6H_4CH_3$), 2.12, 2.03 (2s, 6H, $2 \times COCH_3$). ESI MS *m*/*z* 481.1 [M+Na].
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31. *Ethyl 2-O-acetyl-3,4-di-O-isopropylidene-1-thio-β-L-fucopyranoside* (**20**). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.93 (dd, 1H, $J_{1,2} = 10.2$ Hz, $J_{2,3} = 7.2$ Hz, H-2); 4.25 (d, 1H,

$J_{1,2} = 10.2$ Hz, H-1); 4.15 (dd, 1H, $J_{2,3}$, $J_{3,4} = 1.8$ Hz, H-3); 4.01 (dd, 1H, $J_{3,4}$, $J_{4,5} = 5.1$ Hz, H-4); 3.81 (m, 1H, H-5); 2.65 (m, 2H, S–CH_2–CH_3); 2.04 (s, 3H, COCH_3); 1.50, 1.29 (2s, 6H, isopropylidene–CH_3), 1.35 (d, 3H, $J_{5,6} = 6.6$ Hz, H-6); 1.19 (t, 3H, $J = 7.5$ Hz, S–CH_2–CH_3). ESI MS m/z 313.1 [M+Na].

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