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Note

$HClO_4$–SiO_2 catalyzed per-*O*-acetylation of carbohydrates☆

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Abstract—An efficient per-*O*-acetylation of carbohydrates catalyzed by $HClO_4$–SiO_2 is reported using a stoichiometric quantity of acetic anhydride avoiding the use of pyridine and excess acetic anhydride under solvent-free conditions.

Keywords: Acetylation; $HClO_4$–SiO_2; Carbohydrates; Stoichiometric; Solvent-free

The application of heterogeneous catalysts such as inorganic solid acids in organic synthesis is an attractive area of research.[1] Several inorganic acids such as montmorillonite clays,[2] zeolites,[3] and nafion-H,[4] have been used as effective catalysts for various organic transformations. The advantages of these heterogeneous catalysts over the homogeneous catalysts include stability, insensitivity towards air and moisture, ease of handling, lack of corrosion and other environmental hazards, and ease of recovery and regeneration.

Per-*O*-acetylation is one of the most commonly used techniques for the protection of hydroxyl groups in carbohydrates. Per-*O*-acetylated sugars are inexpensive and useful intermediates for the synthesis of naturally occurring glycosides, oligosaccharides and other glycoconjugates.[5] Structural elucidations of many natural products containing carbohydrates have been confirmed by transforming them into their per-*O*-acetates. Acetylation of sugars is often carried out using a large excess of acetic anhydride as the reagent and solvent and the catalysts employed include pyridine,[6] sodium acetate,[6] sulfuric acid[7] and perchloric acid.[8] Pyridine is the most widely used despite of its toxicity and unpleasant odor.[9] In some cases, pyridine derivatives, for example, 4-(*N*,*N*-dimethylamino)pyridine and 4-(pyrrolidino)pyridine have been used as a cocatalysts to speed up the reactions.[10] A variety of other catalysts, in combination with excess acetic anhydride and solvents have been employed in the *O*-acetylation of carbohydrates and non-carbohydrates, including zinc chloride,[11] iron(III) chloride,[12] ion exchange resin,[13] iodine,[14] scandium triflate,[15] copper triflate,[16] trifluoromethanesulfonate triflate,[17] indium triflate,[18] and bismuth triflate.[19] In many cases, these reactions require extended reaction times and the use of excess acetic anhydride as the solvent sometimes causes troublesome workup during the neutralization process. Recently, acetylation has been achieved via indium chloride in conjunction with microwave irradiation;[20] however, an excess of acetic anhydride is required. Despite the number of available methods, there is a need to develop a fast clean reaction protocol for the per-*O*-acetylation of sugars using an economically convenient heterogeneous catalyst and a stoichiometric quantity of acetic anhydride.

Prompted by a recent report[21] on the $HClO_4$–SiO_2 catalyzed acetylation of simple alcohols, a series of monosaccharides, disaccharides and trisaccharides have been successfully per-*O*-acetylated in the presence of a stoichiometric quantity of acetic anhydride and a catalytic amount of $HClO_4$–SiO_2 (25 mg/mmol of free sugar) under solvent free conditions within a few minutes. In earlier report, $HClO_4$ catalyzed the acetylation reaction using a large excess of acetic anhydride at extended

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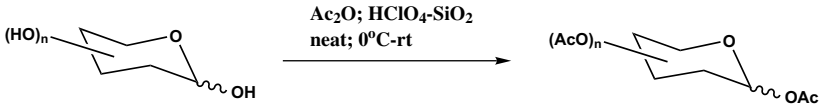


Scheme 1.

reactions times.[8] To avoid the presence of water in the reaction medium, which certainly has a deleterious effect on the formation of product, $HClO_4$ has been impregnated on silica gel, which also increases the effective surface area of the catalyst. $HClO_4$–SiO_2 acted as an inexpensive insoluble catalyst, which could be removed from the reaction mixture by simple filtration. The catalyst is a non-corrosive free flowing powder, which can be stored at room temperature for several months without losing its catalytic activity. Although $HClO_4$ acetic anhydride mixtures are known to explode, we had no problems handing this reagent.

In most cases clean formation of the products was observed. However, for the preparation of analytical samples of the product, the crude reaction mixture was passed through a short pad of silica gel using hexane–ethyl acetate as the eluant. With the hydrated sugars, a slight decrease in the yield was observed, which may be due to the partial consumption of acetic anhydride by the water present in the starting materials. Products of all known compounds gave acceptable ^1H NMR and ^{13}C NMR spectra that matched the data reported in the cited references. In the case of reducing sugars, per-*O*-acetylation gave a mixture of α- and β-acetates, the ratio of which was determined by NMR spectroscopy (Scheme 1).

In conclusion, a fast, simple and convenient methodology has been developed for the preparation of per-*O*-acetylated carbohydrate derivatives using stoichiometric quantity of acetic anhydride avoiding pyridine under solvent-free conditions. A large number of functional groups used for protecting group manipulation of carbohydrates remained unaffected under the reaction condition.

1. Experimental

1.1. General methods[22]

1.2. Preparation of $HClO_4$–SiO_2 catalyst[21]

$HClO_4$ (1.8 g, 12.5 mmol, as a 70% aq solution) was added to a suspension of SiO_2 (230–400 mesh, 23.7 g) in Et_2O (70.0 mL). The mixture was concentrated and the residue was heated at 100 °C for 72 h under vacuum to furnish $HClO_4SiO_2$ (0.5 mmol/g) as a free flowing powder (50 mg = 0.025 mmol of $HClO_4$).

1.3. Typical experimental protocol, 1,2,3,4,6-penta-*O*-acetyl-α,β-D-galactopyranose

A suspension of D-galactose (1.8 g, 10.0 mmol) in Ac_2O (4.82 mL, 51.0 mmol) was placed in an ice bath with continuous stirring. To the cold suspension of the reaction mixture was added $HClO_4$–SiO_2 (250 mg). An exothermic reaction started immediately and the reaction mixture was allowed to stir for an appropriate time as mentioned in the Table 1. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through Celite and evaporated to dryness. The crude reaction mixture was co-evaporated with toluene twice to remove traces of acetic acid and the crude product was purified by column chromatography on silica gel using 3:1 hexane–EtOAc to furnish 1,2,3,4,6-penta-*O*-acetyl-α,β-D-galactopyranose (3.7 g; 95%; α:β = 3:1).

1.4. 1-Propanonyl 2,3,4,6-tetra-*O*-acetyl-β-D-*C*-glucopyranoside (entry 9)

^1H NMR: δ 5.20 (t, J = 9.4 Hz, 1H), 5.03 (t, J = 9.4 Hz, 1H), 4.88 (t, J = 9.4 Hz, 1H), 4.28–4.19 (dd, J = 12.4, 5.0 Hz, 1H), 4.06 (d, J = 2.0 Hz, 1H), 4.02–3.90 (m, 1H), 3.72–3.56 (m, 1H, H-5), 2.80–2.68 (dd, J = 25.4, 8.8 Hz, 1H), 2.52–2.42 (dd, J = 16.6, 3.2 Hz, 1H), 2.18 (s, 3H, CH_2COCH_3), 2.06, 2.04, 2.02, 2.00 (4 s, 12H, 4 $COCH_3$). FABMS: *m*/*z* 389 [M+1]; Anal. Calcd for $C_{17}H_{24}O_{10}$: C, 52.57; H, 6.23. Found: C, 52.48; H, 6.30.

1.5. 2,3,4,6-Tetra-*O*-acetyl-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-α-D-glucopyranoside (entry 15)

^1H NMR: δ 5.49 (t, J = 9.8 Hz, 2H, H-2, H-2′), 5.28 (d, J = 3.6 Hz, 2H, H-1, H-1′), 5.09 (t, J = 8.7 Hz, 2H, H-3, H-3′), 5.02 (t, J = 8.7 Hz, 2H, H-4, H-4′), 4.22–3.92 (m, 6H, H-5, H-5′, H-6, H-6′), 2.09, 2.08, 2.04, 2.03 (4s, 24H, 8 $COCH_3$). FABMS: *m*/*z* 679 [M+1]. Anal. Calcd for $C_{28}H_{38}O_{19}$: C, 49.56; H, 5.64. Found: C, 49.47; H, 5.72.

1.6. 2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-acetyl-α-D-glucopyranosyl-(1→2)-1,3,4,6-tetra-*O*-acetyl-β-D-fructofuranose (entry 17)

^1H NMR: δ 5.67 (d, J = 3.5 Hz, 1H), 5.48–5.44 (m, 3H), 5.38–5.30 (m, 2H), 5.13 (br s, 1H), 5.11–5.00 (m, 2H), 4.77 (dd, J = 9.0, 3.0 Hz, 1H), 4.42–4.23 (m, 5H),

Table 1. $HClO_4$–SiO_2 catalyzed per-*O*-acetylation of carbohydrates using a stoichiometric quantity of acetic anhydride[a]

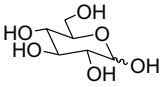
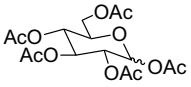
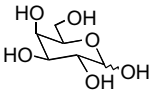
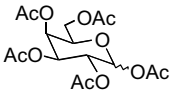
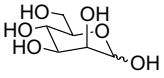
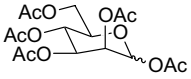
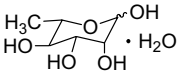
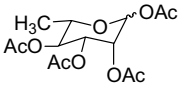
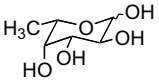
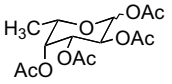
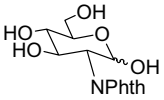
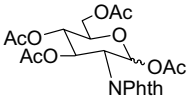
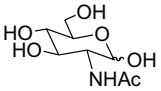
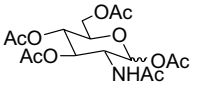
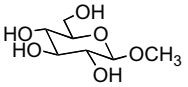
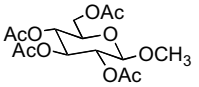
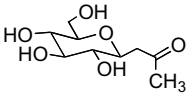
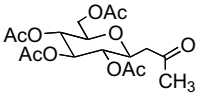
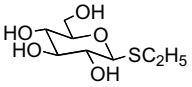
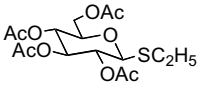
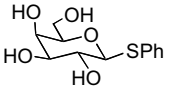
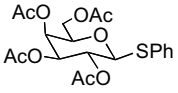
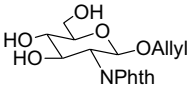
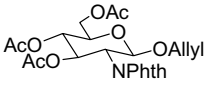
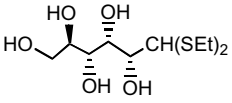
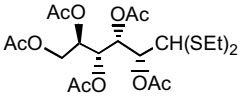
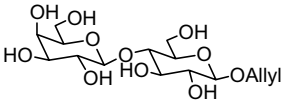
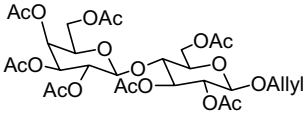
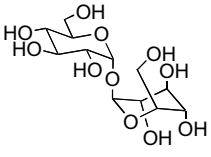
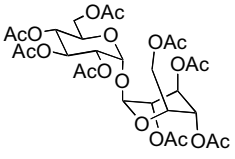
Entry	Sugars	Products	Time (min)	Ac_2O (equiv)	Yield (%)	Refs.
1			5	5.1	92 α/β: 3.3:1	16
2			5	5.1	95 α/β: 3:1	16
3			3	5.1	90 α/β: 2:1	16
4			5	5.0	85 α/β: 2.5:1	16
5			5	4.1	85 α/β: 3.3:1	16
6			15	4.1	90 α/β: 1:2	23
7			20	4.1	92 α/β: 1:0	24
8			5	4.1	95	25
9			5	4.1	92	26
10			5	4.1	92	27
11			5	4.1	95	28
12			5	3.1	90	29
13			5	5.1	96	30
14			5	8.1	90	31
15			10	8.1	90	—

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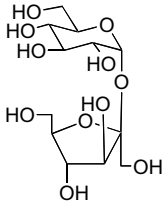
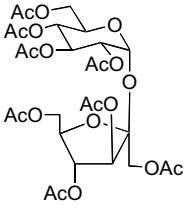
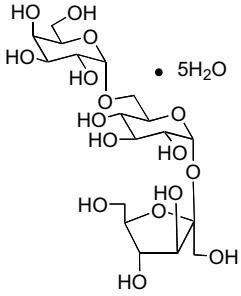
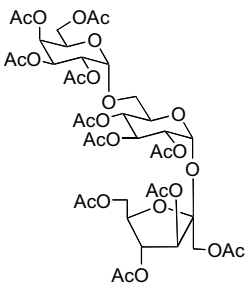
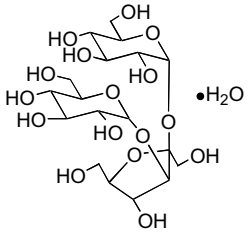
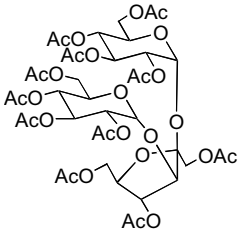
Table 1 (*continued*)

Entry	Sugars	Products	Time (min)	Ac_2O (equiv)	Yield (%)	Refs.
16			10	8.1	92	32
17			10	16	87	—
18			10	12	85	—

[a] Products of all known compounds gave ^{1}H NMR and ^{13}C NMR spectra that matched data reported in the cited references. New compounds were characterized as outlined in the experimental section.

4.17–4.12 (m, 2H), 4.10–4.00 (m, 2H), 3.82–3.70 (m, 1H), 3.62–3.50 (m, 1H), 2.18, 2.15, 2.13, 2.12, 2.11, 2.10, 2.06, 2.02, 1.96 (9s, 33H, 11 $COCH_3$). FABMS: *m*/*z* 967 [M+1]. Anal. Calcd for $C_{40}H_{54}O_{27}$: C, 49.69; H, 5.63. Found: C, 49.77; H, 5.75.

1.7. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl-(1→3)-[(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1→2)]-1,4,6-tri-*O*-acetyl-β-D-fructofuranose (entry 18)

^{1}H NMR: δ 5.76 (d, J = 3.8 Hz, 1H), 5.48 (t, J = 8.5 Hz, 2H), 5.39 (dd, J = 9.8, 2.8 Hz, 2H), 5.29 (d, J = 3.9 Hz, 1H), 5.19–5.12 (m, 2H), 5.0 (dd, J = 9.6, 3.5 Hz, 1H), 4.85 (dd, J = 9.4, 3.4 Hz, 1H), 4.44–4.38 (m, 3H), 4.32–4.29 (m, 4H), 4.25–4.18 (m, 2H), 4.12–4.05 (m, 2H), 2.13, 2.11, 2.08, 2.04, 2.0 (5s, 33H, 11 $COCH_3$). FABMS: *m*/*z* 967 [M+1]. Anal. Calcd for $C_{40}H_{54}O_{27}$: C, 49.69; H, 5.63. Found: C, 49.80; H, 5.72.

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