Vinyl acetate and sodium carbonate as a fast and efficient catalyst for per-*O*-acetylation of monosaccharides†

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Vinyl acetate and sodium carbonate catalysed acetylation of several monosaccharides is an efficient synthesis of per-*O*-acetylation of carbohydrates and achieve the products in excellent yields and short reaction times. D-Glucose as the substrate in large scale also proceeds in high yield.

Keywords: vinyl acetate, sodium carbonate, per-*O*-acetylation, monosaccharides

The protection of alcohols with an acetyl group is one of the most common transformations in organic synthesis. Per-*O*-acetylation is one of the most frequently used reactions in carbohydrates primarily for initial protection of sugars and also to aid spectral characterisation and identification of target molecules. One of the widely used protocols for protecting carbohydrate alcohols with acetic anhydride requires pyridine[1,2] as both the solvent and catalyst, despite its known toxicity and unpleasant odour.[3,4] Further addition of pyridine derivatives, such as, 4-(dimethylamino)pyridine and 4-(1-pyrrolidino)pyridine as a co-catalyst speeds up this transformation. Besides this, Wolfrom's anhydrous sodium acetate method[5] is still the choice for the stereoselective preparation of β-glycosyl acetates. Other acetylation methods use $Sc(OTf)_3$,[6] $Cu(OTf)_3$,[7] $CoCl_2$,[8] I_2,[9] $InCl_3$,[10] $BF_3{\bullet}OEt_2$[11,12] as the catalyst. However, most of these procedures have their own disadvantages, such as, excess of acetic anhydride causes tedious workup in the neutralisation process, pyridine is restricted due to health hazards, heavy metal salt use is also restricted for health reasons and environmental pollution. Furthermore, these methods have other drawbacks such as long reaction time, use of costly catalysts and reagent and the health hazard of catalysts and reagent.

Thus, a new catalyst would be indispensable for acetylating alcohols[13-16] particularly if it led to easy purification, short time and high transformation. Recently, per-*O*-acetylation using vinyl acetate as an acetylating reagent for alcohols has been reported.[17-19] Among these alcohols, only a few carbohydrates were proposed in the literature. Meanwhile, most reports require expensive lipase as the catalyst[20] which could not completely catalyse the acetylation and may lose the enzymatic activity during the process. However, chemical acetylation with vinyl acetate on carbohydrates is a very promising approach.

In the recent literature, chemical acetylation of cellulose with vinyl acetate has been disclosed,[21] with DMSO as solvent and tetrabutylammonium fluoride trihydrate as catalyst. Although the reaction is achieved in a short time and high yield, the catalyst is expensive and only partially acetylated carbohydrate was obtained. Two references described a base catalysing acetylation of sucrose[22] and starch[23] with vinyl acetate in water. The reaction system is insensible to water and oxygen, which is convenient in the operation, but also vinyl acetate is cheap and nontoxic. Therefore this idea is worth further research.

We report here a novel, mild and efficient per-*O*-acetylation with vinyl acetate catalysed by sodium carbonate at room temperature in a short time and with a high yield; sodium carbonate is also quite a cheap catalyst.

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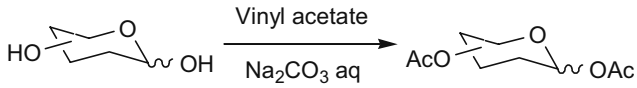
† Dedicated to Professor Yongzheng Hui on the occasion of his 70th birthday.



Scheme 1 Per-*O*-acetylation of monosaccharides in sodium carbonate and vinyl acetate

Results and discussion

When attempting to complete the acetylation of carbohydrate, our team first tried the base catalysed acetylation of monosaccharides with vinyl acetate in water. In the reaction to prepare D-glucopyranosyl pentaacetate, NaOH as the catalyst,[22] per-*O*-acetate of D-glucose was obtained very quickly but partial acetate of D-glucose also formed. Apparently, the reaction system catalysed by NaOH is too alkaline, hence both acetylation and hydrolysis proceeded quickly. While reaction system catalysed by NaOAc, a much weaker base, resulted in low yield and even prolonged the reaction time due to the weak alkaline conditions.

After a series of experiments, we found the following interesting phenomena. If the pH of reaction system is too low (<8), the acetylation cannot be completed even through extending the reaction time. If the pH of the system is too high (>10), the product and even the reagent will be hydrolysed rapidly during the process. With all these considerations, it is crucial to find a suitable base as the catalyst. After numbers of comparisons of inorganic bases, we discovered that sodium carbonate and potassium carbonate gave the optimum pH 9. Since sodium carbonate is cheaper than the potassium salt, it is a suitable catalyst for further scale-up syntheses.

As shown in Table 1, the reaction catalysed by sodium carbonate gave high yields in a very short time. A series of peracetylated monosaccharides were synthesised with the vinyl acetate and the pH of the system was adjusted by sodium carbonate to 9 in water. Further exploration of this reaction system suggests that the use of a little water at the beginning stage of the reaction may not be necessary, since the reaction itself will generate water. For comparison, per-*O*-acetylation of monosaccharides was also carried out without adding water. These reactions also gave high yields in very short times as expected (Table 1).

We also studied the impact of base concentration on the reaction. The results of per-*O*-acetylation of D-glucose catalysed by the different concentration of sodium carbonate are summarised in Table 2. From the Table 2, we can tell that 10%(w/v) of the concentration is the optimal condition. Also 2.5%, 5%, 7.5% and 12.5% of the concentration displayed similar results in high yields. After these preliminary experimental results, we discovered that 2.5%, 5.0% and 7.5% cannot be sufficient to catalyse the reaction completely, while 12.5% and 15.0% resulted in the product hydrolysis during the process.

Since the reaction system gave high yields even the reaction system was dry in the prophase, this makes the scale-up

Table 1 Na_2CO_3 catalysed monosaccharides with vinyl acetate

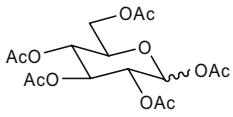
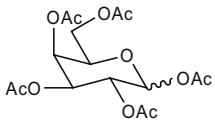
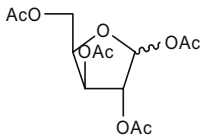
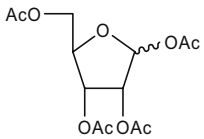
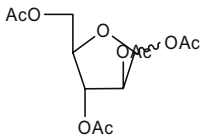
Entry	Monosaccharide	Product	Time/min	Yield/% in water	α:β	Yield without water	α:β	Ref.
1	D-glucose		40	100	2.6:1	100	2.3:1	12
2	D-galactose		70	100	1.7:1	100	1.8:1	12
3	D-xylose		50	96.5	1:1	92.7	0.88:1	23
4	D-ribose		40	92.8	1:1	92.6	1:1	23
5	D-arabinose		30	98.4	1:1	94.5	0.89:1	23

Table 2 Different concentration of sodium carbonate catalysed per-*O*-acetylation of D-glucose

Entry	Concentration/w/v	Time/min	Yield/%	α:β
1	2.5	60	90.1	2.0:1
2	5.0	50	91.4	2.1:1
3	7.5	50	92.6	2.2:1
4	10.0	40	100.0	2.6:1
5	12.5	70	93.2	2.0:1
6	15.0	80	82.0	2.1:1

operation convenient. The results of per-*O*-acetylation of D-glucose **1** could reach complete reaction on a large scale are shown in Table 3. A 10-fold, 20-fold and even 100-fold enlargement for the reaction shown similar results, although the reaction time needs to be prolonged. The reaction is exothermic, hence in the large-scale preparations, it is advisable to add the base dropwise in an ice bath.

Conclusion

In conclusion, the combination of the vinyl acetate and sodium carbonate is a cheap and green system for per-*O*-acetylation of monosaccharides at excellent yields with a short reaction time and easy workup. We believe that this method would find a wide application in the protection of saccharides and other processes.

Experimental

^{1}H NMR spectra were recorded on a Bruker DRX-500 MHz spectrometer using tetramethylsilane as internal standard and $CDCl_3$ as solvent. Mass spectra were detected on Agilent 5973N EI mass spectrometer. All the reagents were purchased with purity of AR. Silica gel (10–40μm, Yantai, China) was used for column chromatography. All the chromatography solvents were distilled before use. TLC plates (10–40μm, Yantai, China) were applied to monitor the reactions. The boiling range of petroleum ether (PE) is 60–90ºC.

Table 3 Per-*O*-acetylation of D-glucose on the large scale

Entry	quantity of D-glucose/g	Time/h	Yield/%
1	1	1.5	100.0
2	2	2	100.0
3	10	3	100.0

General procedure for acetylation of D-glucose on a small scale

(1) 0.100 g (0.56 mmol) D-glucose was dissolved partially with 0.1 ml distilled water in a 10 ml flask. 0.75 ml (8.1 mmol, 2.9equiv.) vinyl acetate was added to the mixture. Aqueous sodium carbonate (10%, w/v, ~7 ml) was added dropwise in order to adjust pH of the system to 9. After completion of the reaction [monitored by TLC, PE: ethyl acetate (EA) = 1 : 1], 20 ml EA was added to extract the product. The EA phase was washed with water, then washed with saturated brine and dried with sodium sulfate anhydrous. The crude product was concentrated and subjected to flash column chromatography. 1, 2, 3, 4, 6-penta-*O*-acetyl-α,β-D-glucopyranose was obtained (0.217 g, 100%, α : β = 2.6 : 1).

(2) 0.100 g (0.56 mmol) D-glucose was dissolved in a 10 ml flask. 0.75 ml (8.1 mmol, 2.9equiv) vinyl acetate was directly added to the mixture. Aqueous sodium carbonate (10%, w/v, ~7 ml) was added dropwise in order to adjust pH of the system to 9. After completion of the reaction (monitored by TLC, PE: EA = 1 : 1), 20 ml EA was added to extract the product. The EA phase was washed with water, then washed with saturated brine and dried with sodium sulfate anhydrous. The crude product was concentrated and subjected to flash column chromatography. 1, 2, 3, 4, 6-penta-*O*-acetyl-α,β-D-glucopyranose was obtained (0.217 g, 100%, α:β = 2.3:1).

^{1}H NMR(500 MHz, $CDCl_3$): δ6.35 (d, *J* = 4 Hz, 0.72H, 1-H), 5.75(d, *J* = 8 Hz, 0.28H, 1-H), 5.50(t, *J* = 10 Hz, 0.72H), 5.27(t, *J* = 10 Hz, 0.28H), 5.10–5.20 (m, 2.05H), 4.28–4.32(m, 1.06H), 4.10–4.15(m, 1.83H), 3.82–3.88(m, 0.29H), 2.05–2.20(5 s, 15H). EIMS: *m/z* 331 (M-OAc, 15), 242 (44), 200 (57), 169 (51), 157 (78), 140 (40), 115(100), 98 (58).

Acetylation of D-galactose (0.217 g with water, 0.217 g without water): ^{1}H NMR(500 MHz, $CDCl_3$): δ6.39 (s, 0.60H, 1-H), 5.72(d, *J* = 8 Hz, 0.40H, 1-H), 5.52(s, 0.65H), 5.44(d, *J* = 2 Hz, 0.41H), 5.32–5.38(m, 1.81H), 5.15(dd, *J* = 10, 3 Hz, 0.53H), 4.32–4.37(m, 0.89H), 4.12–4.20(m, 2.80H), 2.00–2.20(5 s, 15H). EIMS: *m/z* 331 (M-OAc, 15), 242 (44), 200 (57), 169 (51), 157 (78), 140 (40), 115(100), 98 (58).

Acetylation of D-xylose (0.206 g with water, 0.197 g without water): ^{1}H NMR(500 MHz, $CDCl_3$): δ6.27 (d, *J* = 3 Hz, 0.50H), 5.73(d, *J* = 8 Hz, 0.50H), 5.48(t, *J* = 10 Hz, 0.51H), 5.22(t, *J* = 8 Hz, 0.49H), 4.98–5.08(m, 2.09H), 4.13(dd, *J* = 11, 5 Hz 0.54H), 3.92(dd, *J* = 11, 6 Hz, 0.56H), 3.71(t, *J* = 11 Hz, 0.56H), 3.50(dd, *J* = 12, 8 Hz, 0.51H), 2.00–2.20 (4 s, 12H). EIMS: *m/z* 259 (M-OAc, 39), 199(29), 170 (79), 157 (49), 139 (40), 128 (100), 115 (40), 97(33), 86 (24).

Acetylation of D-ribose (0.198 g with water, 0.199 g without water): ^{1}H NMR(500 MHz, $CDCl_3$): δ6.04 (d, *J* = 4 Hz, 0.50H), 5.48(t, *J* = 7 Hz, 0.50H), 5.32–5.37(m, 0.50H), 5.14–5.18 (m, 0.62H), 5.01–5.05(m, 0.50H), 4.32–4.38(m, 0.50H), 4.16(dd, *J* = 12, 6 Hz, 0.25H), 4.00–4.05 (m, 0.60H), 3.92(dd, *J* = 13, 5 Hz, 0.53H), 3.72–3.76(m, 0.42H), 2.05–2.20(4 s, 12 H) EIMS: *m/z* 259 (M-OAc, 39), 199(29), 170 (79), 157 (49), 139 (40), 128 (100), 115 (40), 97(33), 86 (24).

Acetylation of D-arabinose (0.210 g in water, 0.201 g without water): ^{1}H NMR(500 MHz, $CDCl_3$): δ6.35 (d, *J* = 3 Hz, 0.46H), 5.68(d, *J* = 7 Hz, 0.54 H), 5.40(d, *J* = 1 Hz, 0.54H), 5.37–5.39(m, 0.86H), 5.28–5.32(m, 1.12H), 5.12(dd, *J* = 9, 2 Hz, 0.57H), 4.37–4.42(m, 0.37H), 4.05–4.09(m, 1.06H), 3.82(dd, *J* = 13, 2 Hz 0.48H), 3.79 (dd, *J* = 13, 2 Hz, 0.57H), 2.00–2.20(4 s, 12H). EIMS: *m/z* 259 (M-OAc, 39), 199 (29), 170 (79), 157 (49), 139 (40), 128 (100), 115 (40), 97(33), 86 (24).

General procedure for scetylation of D-glucose on a large scale

(1) 1 g (5.6 mmol) D-glucose was added to 7.5 ml (8.1 mmol, 2.9equiv) vinyl acetate in a 100 ml flask. Aqueous sodium carbonate (10%, w/v, 60 ml) was added dropwise in an ice bath in order to adjust the pH of the system to 9. After completion of the reaction (monitored by TLC, PE: EA = 1 : 1), 60 ml EA was added to extract the product. The EA phase was washed with water, then washed with saturated brine and dried with sodium sulfate anhydrous. The crude product was concentrated and subjected to flash column chromatography. 1,2,3,4,6-penta-*O*-acetyl-α,β-D-glucopyranose was obtained (2.17 g, 100%).

(2) 2 g (11.1 mmol) D-glucose was added to 15 ml (16.2 mmol, 2.9equiv) vinyl acetate in a 250 ml flask. Aqueous sodium carbonate (10%, w/v, 120 ml) was added dropwise in an ice bath in order to adjust the pH of the system to 9. After completion of the reaction (monitored by TLC, PE: EA = 1 : 1), 120 ml EA was added to extract the product. The EA phase was washed with water, then washed with saturated brine and dried with sodium sulfate anhydrous. The crude product was concentrated and subjected to flash column chromatography. 1,2,3,4,6-penta-*O*-acetyl-α,β-D-glucopyranose was obtained (4.34 g, 100%).

(3) 10 g (56 mmol) D-glucose was added to 75 ml (81 mmol, 2.9equiv) vinyl acetate in a 1000 ml flask. Aqueous sodium carbonate (10%, w/v, 600 ml) was added dropwise in an ice bath in order to adjust the pH of the system to 9. After completion of the reaction (monitored by TLC, PE: EA = 1:1), 600 ml EA was added to extract the product. The EA phase was washed with water, then washed with saturated brine and dried with sodium sulfate anhydrous. The crude product was concentrated and subjected to flash column chromatography. 1,2,3,4,6-penta-*O*-acetyl-α,β-D-glucopyranose was obtained (21.7 g, 100%).

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