Solvent-Free Per-*O*-acetylation of Carbohydrates

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A facile, solvent-free acetylation method promoted by commercial 4Å molecular sieves is described here for the synthesis of per-*O*-acetylated carbohydrates, which are important intermediates in carbohydrate chemistry. Several examples of carbohydrate and noncarbohydrate substrates are provided.

Keywords: Green chemistry, Acylation, Carbohydrates, Molecular sieves.

INTRODUCTION

Acetylation is one of the most frequently used reactions in carbohydrate chemistry and it provides an efficient method for protecting hydroxyl groups. In particular, peracetylated carbohydrates are important and useful intermediates in the chemical synthesis of complex carbohydrates, especially for chemical glycosylations (**Scheme-I**). Peracetylated sugars can be used as a glycosylation donor directly¹⁻² catalyzed by Lewis acid. Also, peracetylated sugars can be further converted to more reactive donors, such as thioglycosides (Fischer donor) or glycosyl halides (Koenigs and Knorr donor)³⁻⁴. Additionally, following selective anomeric deacetylation of the peracetylated sugar, Schmidt donor trichloroacetimidate can be prepared⁵. More importantly, the stereochemical outcomes of these glycosylation reactions are often affected/controlled by the neighboring group participation of the C-2 acetate. Recently, peracetylation has been widely used to enhance the bioavailability and cell membrane permeability of carbohydrates, which are crucial for their applications in current chemical glycobiology⁶⁻⁹. Once the molecule is inside the cell, the acetyl groups are readily cleaved by nonspecific esterases.

Classic peracetylation of carbohydrates requires pyridine as the solvent as well as a base to promote the acylation process. However, pyridine is toxic and possesses offensive odor. It also makes TLC appear like a huge smear and often complicates the reaction work-up and product purification. Therefore, more attention has been placed on performing acylation under solvent-free conditions^{10,11} or with some novel catalysts, such as small base molecules¹⁰, ionic liquids¹², molecular iodine¹³,

zeolite¹⁴, and other solid catalysts. For the same reason, we introduce a solvent-free and environmentally benign approach for the preparation of peracetylated carbohydrates promoted by 4Å molecular sieves.

Scheme-I: Peracetylated carbohydrates as important intermediates for chemical glycosylation

EXPERIMENTAL

4Å MS (8-12 mesh, Mallinckrodt Catalogue No. 4494-04, CAS No. 1344-00-9) were used directly from the bottle without drying or activation. Typically, carbohydrate (400 mg), 4Å molecular sieves (2 g) and acetic anhydride (4 mL) were stirred at 90 °C in an oil bath for 4-10 h. The amount of acetic anhydride and molecular sieves was doubled for disaccharide such as lactose. The reaction progress was monitored by TLC chromatography. Upon completion, the reaction mixture was

cooled to room temperature, diluted with EtOAc (40 mL) and filtered to remove the molecular sieves. The filtrate was washed with saturated NaHCO_3 (30 mL $\times$ 3) and brine (30 mL). The organic layer was then dried over anhydrous Na_2SO_4 . The solvent was removed by a rotary evaporator under reduced pressure and the residue was purified by recrystallization or flash silica gel chromatography (hexane/EtOAc) or used directly for subsequent reactions.

RESULTS AND DISCUSSION

Molecular sieves are widely used as a desiccant to dry solvents in chemistry labs. However, the alkalinity character of molecular sieves (*e.g.* 3 Å and 4 Å MS) has also been observed recently, which could potentially promote various organic reactions. For example, selective/complete acetylation

of protected carbohydrates and peracetylation of nucleosides have been achieved by the promotion of molecular sieves^{15,16}. In contrast, due to the alkaline pH of methanol stored over 4 Å or 3 Å molecular sieves, it served as a mild de-*O*-acetylation reagent without adding extra sodium methoxide^{17,18}.

We chose 4 Å MS as the promoting agent because it has been noted to have a more pronounced basic character^{19,20}. The pH of an aqueous slurry of 4 Å molecular sieves (0.05 g/mL) was assessed using pH paper, showing in the range of 9.5–10. Moreover, 4 Å MS is commercially available and relatively inexpensive and the per-*O*-acetylation of carbohydrates with 4 Å MS is unexplored. Satisfyingly, representative carbohydrates were per-*O*-acetylated to the corresponding products in high to moderate yields (Table-1)²¹. All carbohydrate acetates were obtained as a mixture of α/β anomers

TABLE-1
YIELDS^[21] FOR THE MS PROMOTED PERACETYLATION

Entry	Substrate	Product	Reaction Time	Yield (%)
1			3.5 h	90 ^a
			3.5 h	85 ^b
			3.5 h	86 ^c
2			4 h	73 ^a
3			4 h	72 ^a
			7.5 h	93 ^a
4			3.5 h	96 ^a
5			4 h	84 ^a
6			4 h	75 ^a
7			8 h	81 ^a
8			2 h	95 ^a
9			0.5~1 h	86 ^d

^aPurified using silica gel chromatography; ^bPurified by recrystallization from methanol on a 1 g scale; ^cReaction using 3 Å MS and purified using silica gel chromatography; ^dPurified by recrystallization from water

as indicated by TLC and ^1H NMR. As shown, glucose was treated with acetic anhydride in the presence of 4Å MS under elevated temperature (90 °C) and the peracetylation reaction reached to completion within 3.5 h. A 90 % yield was obtained after purification by flash silica gel chromatography (entry-1). This reaction was also carried out on a 1 g scale and 85 % yield was obtained after purification by recrystallization from methanol. Additionally, 3Å MS was checked for the same acetylation and it was found to be as active (86 %, entry-1). In comparison, when molecular sieves were not used, only -20 % of product was detected by TLC at 4 h for glucose acetylation²². The use of alkali metal ions KCl exchanged MS¹⁵ with more weakly basic spots did not demonstrate significant improvement for the reaction time and yields.

Other common monosaccharides, including galactose (Entry-2), L-rhamnose¹ (Entry-3) and D-ribose (Entry-4) were also acetylated in good yields. Elongated reaction time may be necessary for some reactions (*e.g.*, Entry-3, 72 %/4 h *vs.* 93 %/7.5 h; and entry 7, 81 %/8 h) to fully consume the partially acetylated products and increase the reaction yield, presumably indicating lower acidity and weaker activity of the axial -OH group. MS promoted peracetylation also went smoothly on amino sugars *N*-acetylglucosamine (Entry-5, 84 %) and *N*-propionylgalactosamine²³ (Entry-6, 75 %). More importantly, good yield was also observed for disaccharide lactose and it seems the presence of water molecules does not have a negative effect on the reaction (Entry-7, lactose monohydrate, 81 %). Finally, as examples of non-carbohydrates, 1,4-cyclohexanediol (Entry-8) and the phenolic hydroxyl group of salicylic acid (Entry-9) were both successfully acetylated with shorter reaction time.

Conclusion

Long known for their drying capacity, molecular sieves have recently demonstrated utility in synthetic organic procedures. In present study, we have shown that 4Å MS could successfully promote the peracetylation of various carbohydrates and noncarbohydrates in a solvent-free condition. This procedure represents a simple, inexpensive and environmentally-friendly method in organic chemistry. Generally high yields were observed which are comparable to those obtained from classic methods. Intensive research is currently underway to exploit similar properties of other types of molecular sieves (*e.g.* 3Å MS, 13X MS).

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- Yields are isolated yields after chromatography or recrystallization. However, in practice, a simple aqueous work-up is sufficient to afford essentially pure product for subsequent reactions (*e.g.* preparation of other glycosyl donors or glycosylation).
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