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$Sc(OTf)_3$-catalyzed acetolysis of 1,6-anhydro-β-hexopyranoses and solvent-free per-acetylation of hexoses

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Abstract—Acetolysis of 1,6-anhydro-β-hexopyranoses and solvent-free per-acetylation of hexoses with acetic anhydride at room temperature in excellent yields employing 0.5 mol% scandium(III) trifluoromethanesulfonate as an extremely efficient catalyst are, respectively, described here.

1,6-Anhydro-β-hexopyranoses are potent synthons toward the synthesis of oligosaccharides, glycoconjugates, and natural products.[1] Their [3.2.1]bicyclic skeletons ensure that not only two less protecting groups at C1 and C6 are needed than their corresponding pyranoses, but also none of the anomeric isomers are required to be differentiated. After cleavage of the internal acetal, further functional group transformation and glycosylation at the C6 and C1 positions, respectively, can be carried out. Typical acetolysis is mainly used to open the 1,6-anhydro ring via treatment with acetic anhydride in the presence of either excess trifluoroacetic acid at room temperature[2] or a catalytic amount of triethylsilyl trifluoromethanesulfonate (TESOTf) at 0°C.[3] Acetic anhydride acts as both reactant and solvent, which often causes tedious workup in the neutralization processes. Since the traditional Lewis acids (TESOTf, BF_3/OEt_2, $TiCl_4$, etc.) are extremely moisture sensitive, there is a need to search for new catalysts. To tackle these problems, we have explored herein a practical and mild procedure that is applicable to a wide variety of substrates.

Lanthanide and group III metal trifluoromethanesulfonates are known as valuable, water-stable, and reusable Lewis acids.[4] They exhibit excellent catalytic activities in the Diels–Alder reactions,[5] Mukaiyama–aldol reactions,[6,7] Michael reactions,[7] Ferrier rearrangements,[8] Ene reactions,[9] Friedel–Crafts acylations,[10] *O*-glycosylations,[11] allylations,[12] cyanations,[13] ketalizations,[14] esterifications,[15] deacetylations,[16] and so on.[17] We describe herein our studies in acetolysis and acetylation–acetolysis of 1,6-anhydro-β-hexopyranoses with minimum amounts of acetic anhydride at room temperature using 0.5 mol% scandium(III) trifluoromethanesulfonate [$Sc(OTf)_3$] as an extremely efficient catalyst. The conditions and results are illustrated in Table 1. In order to test the compatibility of different protecting groups, the D-*gluco* derivatives **1** and **2** were examined (entries 1 and 2), and the expected products **8**[18] and **9** were isolated in almost quantitative yields, respectively. The reaction rate of compound **2**, which contains three electron-donating protecting groups, is faster than **1**. In entry 3, 1,6-anhydro-β-D-glucopyranose **3** was treated with 4 equiv. of acetic anhydride, and the triacetate **1** was obtained in excellent yield in a very short period. When the amount of acetic anhydride was increased to 12 equiv., one-pot acetylation–acetolysis was successfully carried out in 5 h. In the cases of the D-*manno* (**4**), D-*galacto* (**5**), L-*ido* (**6**),[1a] and L-*altro* (**7**)[1a] sugars, similar results were observed, respectively.[18]

The mechanism of one-pot acetylation–acetolysis of the 1,6-anhydro-β-hexopyranosyl sugars is proposed in Scheme 1. $Sc(OTf)_3$ seems to be involved in two consecutive cycles. In the first acetylation-cycle, acetic anhydride is activated by $Sc(OTf)_3$, perhaps forming a polarized complex **14**, which is then rapidly attacked by the free hydroxyl group of the sugar molecule **15** to generate two charged species **16** and **17**. A rapid proton exchange takes place between the two to furnish the acetate **18** and acetic acid, liberating the Lewis acid in

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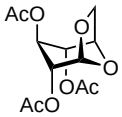
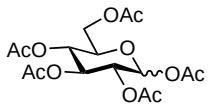
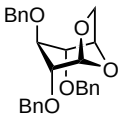
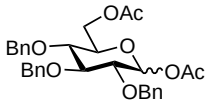
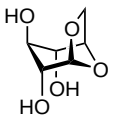
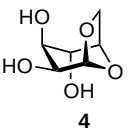
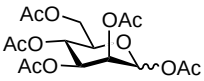
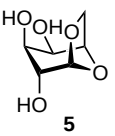
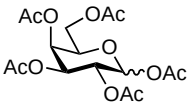
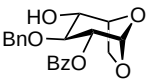
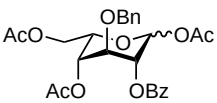
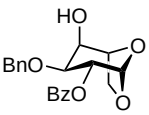
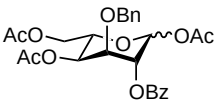
Table 1. $Sc(OTf)_3$-catalyzed acetolysis of 1,6-anhydrohexopyranoses with acetic anhydride at room temperature

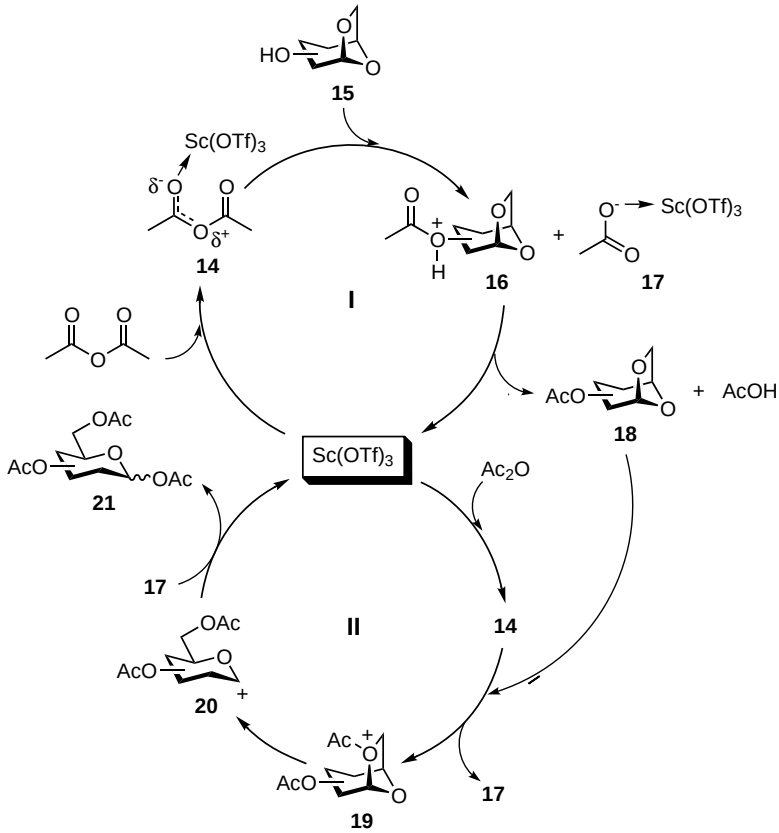
entry	SM	Ac_2O (eq)	t (h)	product	yield (%)
1	 **1**	4	5.5	 **8**	>95
2	 **2**	4	1	 **9**	>95
3	 **3**	4	<0.2	**1**	>95
		12	5	**8**	>95
4	 **4**	15	5	 **10**	>95
5	 **5**	15	5	 **11**	>95
6	 **6**	5	20	 **12**	>95
7	 **7**	5	24	 **13**	>95

its free form. With the data in hand, it appears that the progress of the second acetolysis-cycle needs a higher concentration of acetic anhydride and a prolonged time scale. The ring oxygen atom at C6 captures the acyloin ion from the complex **14** to form the positively charged intermediate **19** and its counter ion **17**. This highly unstable species **19** readily undergoes cleavage of the C1–O6 bond to relieve the ring strain generating a new positive charge at the anomeric center of the pyranosyl compound **20**, which is then readily attacked by **17** to deliver the fully acylated sugar **21** and the Lewis acid in its original form.

$Sc(OTf)_3$-,[15a,b] $In(OTf)_3$-,[15c] $Bi(OTf)_3$-,[15d] or V(O)-$(OTf)_2$-catalyzed[19] esterifications of alcohols with acid anhydrides in a variety of solvents have been reported. However, treatment of D-glucose with acetic anhydride in dichloromethane in the presence of 0.5 mol% $Sc(OTf)_3$ for 2 days afforded a mixture of esters and starting material. Since acetylation of **3** in neat conditions successfully gave the triacetate **1** in excellent yield (Table 1, entry 3), we proceeded to apply this strategy in hexoses (**22**–**26**). The results for solvent-free per-acetylation of sugars with almost stoichiometric amount of acetic anhydride at room temperature employing 0.5 mol% $Sc(OTf)_3$ as the catalyst are summarized in Table 2. In entry 4, when the reaction was carried out at 0°C, the isolated yield of L-fucopyranosyl tetraacetate **27** was improved.

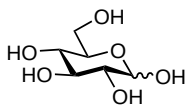
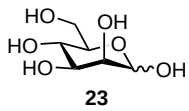
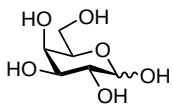
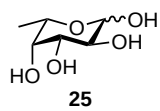
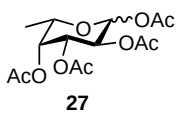
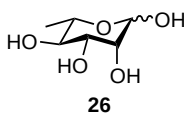
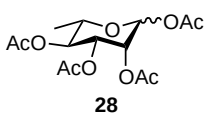
In conclusion, we have successfully developed a practical and convenient route to carry out the $Sc(OTf)_3$-catalyzed acetolysis of 1,6-anhydro-β-hexopyranoses and solvent-free per-acetylation of hexoses in excellent yields.

General procedure of acetolysis and per-acetylation. A mixture of starting material, fleshly dried scandium trifluoromethanesulfonate (0.5 mol%), and acetic anhydride was stirred at room temperature under nitrogen



Scheme 1.

Table 2. $Sc(OTf)_3$-catalyzed solvent-free per-acetylation of hexoses with acetic anhydride at room temperature

entry	hexose	t (h)	Ac_2O (eq.)	product	yield (%)
1	 **22**	4.5 1.5	5.1 6	**8**	99 96
2	 **23**	1	5.1	**10**	91
3	 **24**	6.5	5.1	**11**	88
4	 **25**	<10min 4.5	4.1 4.1	 **27**	78 92[a]
5	 **26**	0.5	5	 **28**	97

[a] The reaction was carried out at 0 °C.

atmosphere. The amount of acetic anhydride and reaction time are listed in Tables 1 and 2. After the reaction is done, methanol was added to quench the rest of acetic anhydride, and the whole solution was kept stirring at room temperature for another 0.5 h. The resulting mixture was concentrated in vacuo to remove methyl acetate and acetic acid, and the residue was dissolved in ethyl acetate followed by sequential wash with saturated sodium bicarbonate aqueous solution, water, as well as brine. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo to afford the expected product in excellent yield.

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18. The spectral data of our compounds corroborated well with the reported ones. The selected physical data of new compounds is listed. Compound **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15–8.12 (m, 1.9H, ArH), 8.10–8.07 (m, 3.0H, ArH), 7.63–7.58 (m, 2.4H, ArH), 7.49–7.44 (m, 5.3H, ArH), 7.41–7.34 (m, 12.3H, ArH), 6.23 (s, 1.4H), 6.21 (d, J=1.7 Hz, 1.0H), 5.31 (ddd, J=3.2, 1.6, 0.8 Hz, 0.9H), 5.22 (dt, J=2.4, 1.2 Hz, 1.5H), 5.00 (ddd, J=2.8, 1.9, 0.8 Hz, 1.5H), 4.94 (ddd, J=2.8, 1.9, 0.8 Hz, 1.0H), 4.83 (d, J=11.8 Hz, 1.7H), 4.79–4.74 (m, 3.6H), 4.62 (dt, J=6.5, 1.7 Hz, 1.5H), 4.47 (ddd, J=7.3, 5.4, 1.9 Hz, 1.0H), 4.33–4.22 (m, 5.4H), 4.01 (t, J=3.0 Hz, 1.0H), 3.92–3.91 (m, 1.5H), 2.11 (s, 5.2H), 2.07 (d, J=0.6 Hz, 11.5H), 1.94 (s, 5.0H), 1.93 (s, 2.8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.46 (C), 169.92 (C), 168.79 (C), 168.60 (C), 165.32 (C), 164.83 (C), 137.33 (C), 136.80 (C), 133.61 (CH), 133.45 (CH), 129.86 (CH), 129.77 (CH), 129.33 (C), 129.06 (C), 128.50 (CH), 128.41 (CH), 128.35 (CH), 128.13 (CH), 127.86 (CH), 127.73 (CH), 127.40 (CH), 91.31 (CH), 90.36 (CH), 73.52 (CH), 72.99 (CH_2), 72.32 (CH_2), 71.85 (CH), 71.67 (CH), 66.72 (CH), 66.30 (CH), 66.07 (CH), 65.87 (CH), 65.54 (CH), 62.23 (CH_2), 62.17 (CH_2), 20.85 (CH_3), 20.76 (CH_3), 20.65 (CH_3), 20.58 (CH_3), 20.55 (CH_3). Compound **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09–8.05 (m, 4.9H, ArH), 7.63–7.59 (m, 2.3H, ArH), 7.49–7.45 (m, 5.2H, ArH), 7.40–7.31 (m, 12.2H, ArH),

6.32 (d, $J=1.7$ Hz, 1.2H), 6.16 (s, 1.0H), 5.48 (dd, $J=4.9$, 1.7 Hz, 1.2H), 5.40 (dd, $J=3.7$, 1.6 Hz, 1.1H), 5.23–5.19 (m, 2.5H), 4.81–4.76 (m, 2.5H), 4.67 (d, $J=2.3$ Hz, 1.6H), 4.64 (d, $J=2.2$ Hz, 0.9H), 4.59–4.55 (m, 1.1H), 4.41–4.31 (m, 4.1H), 4.27 (d, $J=3.0$ Hz, 1.1H), 4.24 (t, $J=2.8$ Hz, 1.2H), 4.21–4.18 (m, 1.8H), 4.15–4.14 (m, 1.1H), 2.11–2.10 (m, 8.2H), 2.09 (s, 3.2H), 2.06 (s, 4.0H), 2.04 (s, 3.4H), 2.01 (s, 3.8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.61 (C), 169.66 (C), 169.61 (C), 168.80 (C), 168.68 (C), 165.33 (C), 164.96 (C), 137.39 (C), 137.06 (C), 133.63 (CH), 133.45 (CH), 129.84 (CH), 129.23 (C), 128.89 (C), 128.46 (CH), 128.41 (CH), 128.35 (CH), 128.08 (CH), 127.94 (CH), 127.66 (CH), 91.21 (CH), 90.27 (CH), 73.24 (CH_2), 72.92 (CH), 72.49 (CH), 72.41 (CH_2), 71.53 (CH), 68.25 (CH), 66.73 (CH), 66.52 (CH), 66.24 (CH), 62.72 (CH_2), 62.52 (CH_2), 20.84 (CH_3), 20.81 (CH_3), 20.69 (CH_3), 20.66 (CH_3).

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