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A green and regioselective acetylation of thioglycoside with ethyl acetate

Pi-Hui Liang *, Yin-Jen Lu, Ting-Hsuan Tang

School of Pharmacy, College of Medicine, National Taiwan University, No. 1, Jen-Ai Road, Section 1, Taipei 100, Taiwan

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ABSTRACT

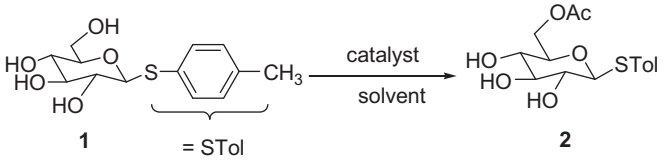
Treatment of saccharidic polyols in ethyl acetate with catalytic sulfuric acid leads to the corresponding primary monoacetate derivatives in good yields. The transesterification was realized by simple stirring without rigorous exclusion of moisture or oxygen. Our protocol is applicable to the regioselective monoacetylation of amino sugars having different substituents at the 2-positions.

Oligosaccharide synthesis is challenging and relies heavily on protecting group manipulations. An efficient, convenient, and regioselective strategy for reaction of the hydroxyl groups would be very useful, particularly if that minimizes the use and generation of hazardous substances.[1] Among the various methods developed for selective acetylation of carbohydrate hydroxyl group,[2] acetic anhydride has been used as a versatile acetylating agent in the presence of bases,[3] molecular sieves,[4] and metal complexes.[5] Alternatively, acetyl chloride was used with a relatively bulky base, for example, 2,4,6-collidine, for selective acetylation of the primary alcohols of carbohydrates at low temperature.[6] Even though the aforementioned methods are effective, the regioselective acetylation must be conducted in strict conditions, for example, reaction temperature and reaction time, to avoid over-acetylation. In addition, removal of acetic acid by-product may also cause problem due to its high boiling point.

To circumvent these problems, other acetylating agents and transesterification with esters have been investigated.[7] Ethyl acetate (EtOAc) is a favorable solvent and diluent because of its low cost, low toxicity, and agreeable odor. The permissible exposure limits (PEL) for EtOAc is 400 ppm, much higher than 5 ppm for acetic anhydride.[8] Selective acetylation of polyols using EtOAc with NaH,[9] neutral alumina,[10] or distannoxane[11] has also been achieved. However, excess NaH must be quenched with aqueous ethanol, such process is potentially dangerous on large scale. On the other hand, it is costly to use a large amount of Al_2O_3 (100-fold weight of the starting alcohol), which had to be removed by filtration. Use of distanoxane compound is disfavored because it is toxic and commercially unavailable. Herein, we describe a simple procedure for the selective acetylation of the primary hydroxyl groups of various carbohydrates by using EtOAc in the presence of a catalyst of sulfuric acid.

Thioglycoside **1** was chosen for our initial study as it is relatively stable, easy to prepare, and widely used as a building block in oligosaccharide synthesis.[12] Several common acids including HCl (aq 37%), H_2SO_4 (aq 96%), HBr (aq 48%), and TMSOTf were examined as the reaction catalyst (Table 1). Regioselective acetylation of the 6-OH group was best conducted by the catalysis of H_2SO_4 (Table 1, entry 3). Thus, nearly complete conversion of **1** was accomplished at 40 °C within 8 h to afford **2** in 72% isolated yield. Under such conditions, no hydrolysis of compound **1** was

Table 1
Selective acetylation of 1-thiotoluene-D-glucopyranoside in different conditions



Entry	Reagents	Catalyst (mol %)	Temp	Time	Yield[a] (%)
1	EtOAc	—	Reflux	4 d	0
2	EtOAc	HCl (20)	60 °C	4 d	45
3	EtOAc	H_2SO_4 (5)	40 °C	8 h	72
4	EtOAc	HBr (10)	40 °C	1 d	72
5	EtOAc	TMSOTf (5)	40 °C	8 h	71
6	EtOAc/H_2O = 10/1	H_2SO_4 (20)	Reflux	2 d	
7	Vinyl acetate	H_2SO_4 (10)	Reflux	1 d	—[b]
8	BzOEt/CH_3CN	H_2SO_4 (10)	80 °C	2 d	18[b]

[a] Isolated yield of **2**.
[b] Complicated mixture.

* Corresponding author. Tel.: +886 23123456x88385.
E-mail address: phliang@ntu.edu.tw (P.-H. Liang).

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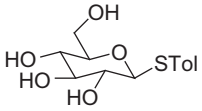
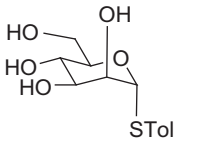
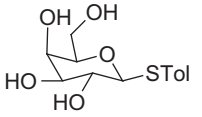
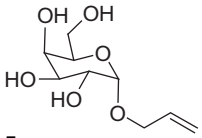
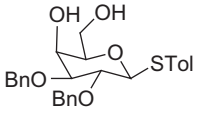
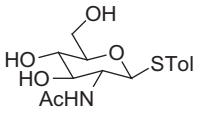
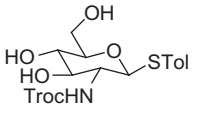
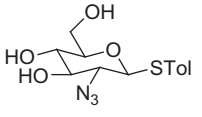
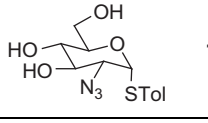
observed. HBr and TMSOTf also effected this transformation, but acetylation in the presence of concentrated HCl required prolonged time for complete conversion and resulted in lower yield (45%) of product. Other acids, including acetic acid, acetyl chloride, $BF_3{\cdot}OEt_2$, HNO_3, TMSCl, TsOH, $LiClO_4$, and Amberlite IR-120 were less active or produced an intractable mixture.

Unlike the previously reported transesterification method that requires anhydrous condition,[7] our current acetylation method could tolerate substantial amount of water. For example, acetylation of **1** in a mixed solvent of EtOAc/H_2O (v/v, 10:1) was effected by the catalysis of H_2SO_4 (10 mol %) to give a 56% yield of product (Table 1, entry 6). Consistent with the effect of acetic anhydride, when EtOAc is used as a solvent, eventual moisture can be eliminated by the solvent itself. The result demonstrates the generality of this method using the commercially available EtOAc without further purification.

Other esters were also tested. Enol ester is a popular acylating agent because the leaving group of enolate readily undergoes tautomerization to ketone (or aldehyde), and thus drives the acylation irreversibly.[13] However, vinyl acetate was unstable under the acidic conditions, and the reaction gave a complicated mixture (Table 1, entry 7). Ethyl benzoate (BzOEt) was also tested for benzoylation. Due to immiscibility of BzOEt with compound **1**, acetonitrile was added as a co-solvent (Table 1, entry 8). Instead of the desired

Table 2
Sulfuric acid-catalyzed selective acetylation of different carbohydrates in EtOAc

Entry	Carbohydrate substrate	Temp (time)	Products[a] (yields, %)			
			6-*O*-Ac	2,6-di-*O*-Ac	3,6-di-*O*-Ac	4,6-di-*O*-Ac
1	 **1**	40 °C (8 h)	72	0[b]	16	8[b]
2	**1**	40 °C (8 h)[c]	71	1.8[b]	14	9.3[b]
3	 **3**	rt (12 h)	83	2.2[b]	2.3[b]	1.9
4	**3**	40 °C (3 h)	72	6.3[b]	6.3[b]	5.4
5	 **4**	40 °C (8 h)	75	1.9[b]	8.6	13[b]
6	 **5**	40 °C (20 h)	72 (70)[d]	4.9[b] (5)[d]	9.7[b] (10)[d]	14 (15)[d]
7	**5**	60 °C (16 h)	65	6.5[b]	11[b]	15
8	 **6**	rt (8 h)	86	—	—	12
9	 **7**	rt (42 h)	88	—	5.6	4.7
10	 **8**	rt (12 h)	90	—	1.9	3.8
11	 **9**	rt (12 h)	95	—	1.1[b]	4.0[b]
12	 **10**	rt (10 h)	93	—	2.1[b]	4.8[b]

[a] The isolated yields of pure products.
[b] The di-*O*-acetates could not be separated, but their ratios were determined by ^1H and 2D-COSY NMR spectral analysis.
[c] TMSOTf (5 mol %) as the catalyst.
[d] Ratio was determined by crude mixture of products by ^1H and 2D-COSY NMR spectral analysis.

benzoylation product, the acetylated compound **2** was obtained in 18% yield, presumably derived by acetonitrile as a source of acetyl group.

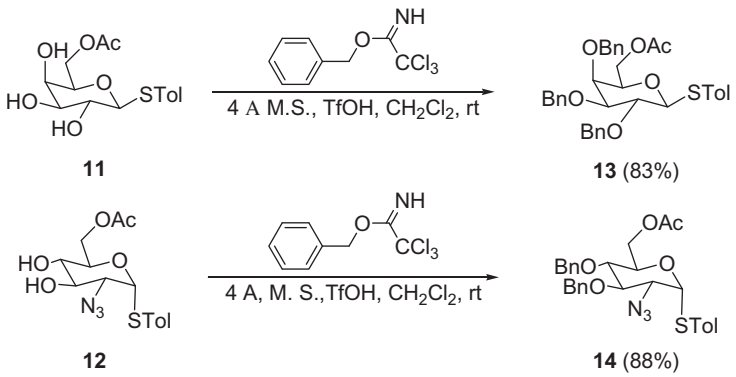
A variety of other saccharidic polyols were subjected to these reaction conditions. In the standard protocol, H_2SO_4 (5–10 mol % of sugar was used) in EtOAc (0.03–0.2 M, Table 2) was added to the carbohydrate substrates with stirring at rt, and the mixture could be warmed to 40–60 °C in appropriate cases.[14] Commercial ACS grade EtOAc was used without purification and the acetylation method needed not to be conducted in inert atmosphere. Although glycosides (e.g., glucoside **1** and galactoside **4**) were only slightly soluble in EtOAc, the reaction still proceeded well to form a homogenous solution at the end of reaction. The reaction mixture was neutralized with saturated $NaHCO_3$, followed by separation, extraction, and distillation of organic solvent. Most of the primary acetate products were obtained by recrystallization, except for the product of **9** which was purified by silica gel column chromatography.

The mother liquor containing diacetate products was further subjected to column chromatography and characterized by ^1H and 2D-COSY NMR spectra. The pure 3,6-di-*O*-acetates derivatives of glucopyranoside **1** and galactosides **4** and **5** were isolated, in addition to the mixture of inseparable 2,6- and 4,6-di-*O*-acetates, whereas the 4,6-di-*O*-acetates of **3** was isolated in addition to the inseparable 2,6- and 3,6-di-*O*-acetates. In the glycoside series (Table 2), the desired 6-acetylated derivatives were obtained as the major products with the yields ranging from 70% to 95%. Regardless of the use of H_2SO_4 or TMSOTf as promoters, the acetylation gave similar yields of isomers (Table 2, entries 1 and 2). Allyl galactoside (Table 2, entry 6) gave similar results to thiogalactoside (Table 2, entry 5), indicating the applicability of this method for other alkyl substituents at C-1 position. In the case of mannoside **3** (Table 2, entries 3 and 4), three regioisomers of diacetates distributed equally, but the 2,6-di-*O*-acetate isomers were the minor products in the gluco- and galacto-pyranoside series (Table 2, entries 1, 2, 5–7) irrespective to the stereochemistry at the anomeric position. This result indicates the feasibility in the regioselective formation of polyol diacetates, which would be useful for the synthesis of complex carbohydrates, for example, 3,6-di-*O*-Ac thioglucoside as the synthetic precursor of saponins.[15] Using higher quantity of catalyst did not increase the yield or reduce the reaction time significantly, but caused inferior selectivity in acetylation. The reaction evaluated temperature could reduce reaction time at the expense of selectivity (Table 2, compared entries 3 and 4, as well as entries 6 and 7). General carbohydrates (e.g., D-glucose) were also subjected to the similar conditions, but the reaction was difficult to proceed due to the solubility problem (data not shown). Very recently, Gervay-Hague and co-workers reported a method by using TMS-protected monosaccharides to increase solubility of general carbohydrates for selective acetylation.[16] TMS-protected monosaccharides might be potential to use in our conditions.

Our reaction protocol is also applied to the regioselective acetylation of various amino sugars, which occur abundantly in natural oligosaccharides with different amino protecting groups. Thus, D-glucosamines derivatives **7**–**10** containing *N*-acetyl (Ac), *N*-trichloroethoxycarbonyl (Troc), and azido groups were prepared,[17,18] and subjected to acetylation in EtOAc by the catalysis of H_2SO_4. To our delight, the regioselective monoacetylated products were furnished at rt in respectable yields (Table 2, 88–95%, entries 9–12).

According to a previous Letter,[19] acetylation of saccharidic polyols may occur at the secondary hydroxyl groups prior to the primary hydroxyl group. In such reaction, counter-ion generated by acetate with two OH groups formed a cyclic transition state.[20] The primary OH group directed the deprotonation toward the secondary OH groups at positions 3 and 4, thus facilitating the acetylation at secondary OH groups. In order to discern if the 6-acetyl compound is obtained by a direct acetylation or derived from the intramolecular transfer of the acetyl groups from the preformed acetates of the secondary hydroxyls, the reaction progress was monitored at ~40% conversion of **5** at 4 h. An aliquot of the reaction mixture was quenched by saturated $NaHCO_3$. According to the 2D-NMR analysis, the mixture was found to contain four monoacetylation products, that is, 2-, 3-, 4-, and 6-*O*-Ac derivatives in a ratio of 11:16:18:54. When the reaction was carried out in a longer time (totally 20 h as that shown in entry 6 of Table 2), the mixture consisted of 2,6-, 3,6-, and 4,6-diacetyl products and the 6-*O*-Ac monoacetyl product in a ratio of 5:10:15:70. No 2-, 3-, and 4-monoacetyl compounds remained. This result indicated that the 2-, 3-, and 4-monoacetyl compounds might undergo intramolecular acetyl group migration to give the 6-*O*-Ac product in a thermodynamically favored process, or undergo the second acetylation subsequently to give the 2,6-, 3,6-, and 4,6-*O*-Ac compounds.

To demonstrate the utility of our protocol, saccharides **11** and **12** having 6-*O*-Ac group were subjected to the acid-catalyzed benzylation with benzyl trichloroacetimidate[21,22] (Scheme 1) to give high yields of **13** and **14**, in which compound **14** is an important intermediate for the synthesis of heparin analogs.[23] In the previously reported methods, four-step procedures are required to prepare **13** and **14**. For example, (1) protection of the 6-OH with a bulky group, such as triphenylmethyl (trityl) or *t*-butyldiphenylsilyl (TBDPS),[24] (2) benzylation of secondary hydroxyl groups, (3) removal of trityl or TBDPS groups, and (4) acetylation of 6-OH. Another four-step procedure includes (1) benzylidene formation of 4,6-dihydroxyls, (2) perbenzylation of secondary hydroxyl groups, (3) selective reduction to reveal free 6-OH group,[25] and (4) acetylation of 6-OH. The overall yield of four steps is usually



Scheme 1. Benzylation of partially acetylated saccharides **11** and **12** by benzyl trichloroacetoimidate in mildly acidic conditions.

lower than 60%. In comparison, our current two-step procedure appears to be superior to the previous four-step procedures in terms of easier operation and higher overall yields.

In conclusion, a green, efficient, and economical protocol for the selective acetylation of carbohydrates has been devised by using EtOAc in the presence of a catalytic amount of sulfuric acid. After simple workup and recrystallization, 6-*O*-acetyl glycosides were obtained in high yields (70–95%). These 6-*O*-acetyl glycosides are useful precursors for the synthesis of complex oligosaccharides. As demonstrated in this study, the acid-catalyzed benzylation of **11** and **12** concluded an expeditious, synthesis of *p*-tolyl-6-*O*-acetate-per-*O*-benzyl thioglycosides **13** and **14**,[23] which are utilized to prepare biologically important substrates.

Acknowledgments

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Supplementary data

Supplementary data (experimental section, spectroscopic data, and copies of ^{1}H, 2D-COSY, and ^{13}C NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.135.

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14. To a solution of 100 mg of glycopyranosides in EtOAc (10 mL) was added a catalytic amount of concentrated H_2SO_4 (aq 96%) at rt. The reaction was warmed to the desired temperature (Table 2). Upon complete acetylation, the mixture was neutralized with saturated $NaHCO_3$ solution (10 mL). The organic layer was separated, and the water layer was washed with EtOAc (5 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated. Except for the reaction of **9** (entry 9, Table 2), the residue was recrystallized from EtOAc/Et_2O (glucopyranoside, entry 1, Table 2) or EtOAc/*n*-hexane (other glycosides) to give 6-*O*-acetyl-glycopyranosides. Separation of di-*O*-acetyl glycopyranosides in and from the reaction of **9** was performed by flash chromatography of mother liquor with elution of EtOAc/*n*-hexane.
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22. To a solution of 6-*O*-acetyl glycoside **11** (or **12**, 0.4 mol) in CH_2Cl_2 (10 mL) were added 4 Å molecular sieves, a freshly prepared solution of benzyl trichloroimidate (0.5 M in *n*-hexane, 2 equiv for each OH), and a catalytic amount of TfOH (0.04 mol). The mixture was stirred at rt for 1 day and then diluted with saturated $NaHCO_3$ (10 mL). The organic layer was separated, and the water layer was washed with EtOAc (5 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated. The residue was subjected to flash chromatography with elution of EtOAc/*n*-hexane to furnish the benzylation products **13** and **14** in 83% and 88% yields, respectively.
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