

$\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$ -catalyzed per-*O*-acetylation of sugars compatible with acid-labile protecting groups adopted in carbohydrate chemistry

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Abstract

Fully acetylated saccharides are inexpensive and very useful starting materials for the synthesis of many naturally occurring glycosides, oligosaccharides, and glycoconjugates. Ferric sulfate hydrate ($\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$) was found to be a valuable Lewis acid promoter in the per-*O*-acetylation reaction of saccharides with acetic anhydride in 100% of conversion rate and 88–99% yields. Interestingly, the procedure is perfectly compatible with the presence of a variety of acid-labile protecting groups, such as isopropylidene, benzylidene, trityl, and TBDMS groups. The reactions were simply performed by stirring the mixture of a sugar with a slight excessive acetic anhydride in the presence of 2.0 mol % of $\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$ at rt and the pure products were obtained by a simple dilution of the reaction mixture with dichloromethane and washings with aqueous Na_2CO_3 .

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1. Introduction

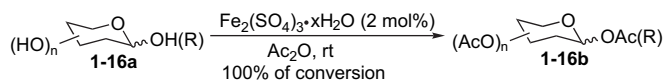
Per-*O*-acetylation is most commonly used for the protection of hydroxyl groups in carbohydrate chemistry. Fully acetylated saccharides are inexpensive and very useful starting materials for the synthesis of many naturally occurring glycosides, oligosaccharides, and glycoconjugates. The structural elucidation of such natural products is very often facilitated by transformation to their per-*O*-acetates of their sugar moieties. Thus, the per-*O*-acetylation of carbohydrates provides a wide range of opportunities for exploitation of precious renewable compounds.

Acetylation of saccharides is invariably carried out using acetic anhydride in the presence of a base or acid catalyst such as pyridine or other amines,¹ sodium acetate,¹ zinc chloride,² ferric chloride,³ toluene sulfonic acid,⁴ montmorillonite,⁵ iodine,⁶ and molecular sieves.⁷ Recently, several triflate derivatives, such as scandium(III) triflate,⁸ trimethylsilyl

triflate,⁹ indium(III) triflate,¹⁰ copper(II) triflate,¹¹ bismuth(III) triflate,¹² lithium triflate,¹³ cerium(III) triflate,¹⁴ were found to be effective as Lewis acid promoters in per-*O*-acetylation of saccharides. However, many of these methods suffer from some drawbacks. The amines and pyridine, which are used as both solvent and a nucleophilic catalyst, present well known toxicity, have unpleasant odors, and are not easy to remove. Handling of large volumes of pyridine and other homogeneous catalysts is troublesome and their recovery is also difficult. Large scale acetylation involving sodium acetate requires special modification of the apparatus to keep the reaction under control.¹⁵ Iodine was shown to be a versatile promoter, the work-up, however, is elaborate and iodine was not recovered. Scandium and indium triflates are expensive catalysts. The cost, availability, toxicity, and difficulty in handling can limit the widespread application of other triflate derivatives. Furthermore, many of these reactions are carried out under reflux, the promoter is used in non-catalytic amounts or tedious work-up is required. Thus, introduction of new efficient methodologies for per-*O*-acetylation reactions of sugars is still in strong demand.

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Scheme 1. Acetylation of sugars catalyzed by $\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$.

In our efforts to develop clean methods for functional group transformations, we found $\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$ was an efficient, reusable, operationally simple, and environmentally benign catalyst for tetrahydropyranylation of alcohols¹⁶ and preparation of acylals.¹⁷ Herein, we present our results on the utility of $\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$ as an efficient and environmentally benign catalyst for the per-*O*-acetylation of a variety of carbohydrates using acetic anhydride (Scheme 1).

2. Results and discussion

We first examined the acetylation of methyl α -D-glucoside (**1a**) with slight excessive acetic anhydride in the presence of 0.5, 1.0, 2.0, 5.0, and 10.0 mol % of $\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$ ¹⁸ at rt. The reactions were completed in 3 h in quantitative conversion rate and 99% isolated yield when the catalyst was used in amount of 2.0–10.0 mol %, while it took longer time (approximately 5 h) when the catalyst was used in amount of 0.5 or 1.0 mol %. Thus, in our method, the acetylation of saccharides was performed in the presence of 2.0 mol % of $\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$.

In view of green chemistry, efficient recovery and reuse of the catalyst are highly preferred. The reusability of the catalyst

was also tested. In our process, $\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$ was easily recovered from the reaction mixture by filtration and subsequent washing with chloromethane. The recovered catalysts were used directly for the next reaction cycle. This recycle protocol was repeated five times and the percentage of the catalyst recovery was always more than 85%, while the yields of the peracetylated glucoside were always more than 95%.

In a typical reaction procedure, $\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$ (2.0 mol %) was added to a stirred suspension of D-glucose (**2a**, 1 mmol) in acetic anhydride (1 mL) at rt and the reaction was monitored using TLC. After 5 h, TLC (ethyl acetate/hexane, 1:1, v/v) showed the presence of only the pentaacetate. The reaction mixture was then diluted with dichloromethane, filtered to recover the $\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$. The combined filtrations were washed with saturated sodium carbonate solution and dried over anhydrous Na_2SO_4 . The solvent was removed to give clear colorless syrup which crystallized on drying under high vacuum (98% yield, nearly quantitative). ¹H NMR spectrum of this product showed it to be a mixture of α -D-glucopyranose pentaacetate with 28% of the β -isomer. The solid was pure peracetylated glucose (**2b**) in 2.5:1 α/β ratio determined by ¹H NMR spectroscopy.

In order to extend the scope of this work, the described methodology was examined on different carbohydrate substrates (Table 1). The reactions were simply performed by stirring the mixture of a sugar with a slight excessive acetic anhydride in the presence of 2.0 mol % of $\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$

Table 1
The peracetylation of saccharidic compounds promoted by $\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$

Entry	Substrate	Product	Time (h)	Yield (%)	α/β
1			3	99	—
2			5	98	2.5:1
3			16	90	3:1
4			5	90	1:1.3
5			5	99	1:1.5
6			15	91	6:1
7			11	97	1.5:1
8			7	89	1:3
9			10	94	1:2.7

(continued on next page)

Table 1 (continued)

Entry	Substrate	Product	Time (h)	Yield (%)	α/β
10			7	89	—
11			7	88	—
12			3	99	—
13			6	99	—
14			30	89	—
15			3	90	—
16			2	97	—

at rt. As shown in Table 1, several monosaccharides (**1a–6a**), disaccharides (**7a–9a**), nucleosides (**10a** and **11a**), and saccharides with acid-labile protecting group (**12a–16a**) were acetylated in excellent yields. It should be outlined the simplicity of the proposed procedure, cheap commercially available reagents being used without resorting to particular experimental precautions. The catalyst can be used without any preliminary activation and recovered by simple filtration. In all cases pure products were obtained by a simple dilution with dichloromethane, filtration to recover the catalyst, and washings with aqueous Na_2CO_3 .

The ratio of α - and β -pyranose anomers for the per-*O*-acetylation products (**2b–9b**) in Table 1 was determined by 400 MHz ^1H NMR spectral analysis. In the case of D-galactose (**3a**), formation of furanose per-*O*-acetate was observed (approximately 9% yield). The peracetylation of substrates **3a**, **6a**, and **14a** needed longer time due to their poor solubility. It is noteworthy that an excellent yield was obtained for per-*O*-acetylated cellobiose (**8a**), which gave only scarce results in other acetylation procedures.^{6,14} Uridine (**10a**) and thymidine (**11a**) were transformed, respectively, into 2',3',5'-tri- and 3',5'-diacetylated products, and the subsequent simple

work-up provided these valuable intermediates for the nucleoside chemistry. NMR spectra confirm that no *N*-acetylated pyrimidine base is present.

In carbohydrate chemistry, some acid-labile groups such as isopropylidene, benzylidene, trityl, and TBDMS ether are often used to protect partial hydroxyl groups in saccharides, and the rest hydroxyl groups are subsequently acetylated. In order to check the efficiency of $\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$ in these cases, we performed reactions of some substrates **12a–16a** using our method. Interestingly, the acid-labile groups such as isopropylidene, benzylidene, trityl, and TBDMS survived the present conditions and the yields of acetylated products were excellent. No formation of fully acetylated compounds was observed. In contrast, in most examples of the above cited acid Lewis promoted acetylations, the cleavage of acid-labile acetal, trityl, and silyl ether functionalities has been reported.

3. Conclusion

In conclusion, we have developed a simple, clean, and efficient method for the per-*O*-acetylation of saccharides. The procedure was shown to be perfectly compatible with a variety

of acid-labile protecting groups adopted in carbohydrate chemistry. The $\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$ was found to be an efficient and environmentally benign heterogeneous catalyst, used in very low percentage, and can be recovered after reaction and reused without significant loss of activity. In addition, a very small amount of acetic anhydride (1 mmol of substrate with 1 mL of acetic anhydride) was used in the procedure compared to other known methods (e.g., using cerium triflate: 1 mmol of substrate with 5 mL of acetic anhydride¹⁴). The simplicity of manipulation, inexpensive and reusable catalyst, excellent yields, compatibility with a variety of acid-labile protecting groups, a very small amount of acetic anhydride usage, and environmentally benign characters make the present method a very good way for per-*O*-acetylation of sugars.

4. Experimental section

4.1. General remarks

All reagents were obtained from commercial sources and used without further purification. Preparation of partially protected sugars (**12a–16a**) followed the known reaction in literatures. The reactions were monitored by TLC on silica gel 60 F₂₅₄ (0.25 mm, E. Merck). ¹H NMR was recorded on Bruker AC-400 NMR spectrometer in solutions of CDCl₃ or DMSO-*d*₆ using tetramethylsilane as the internal standard, δ values are given in parts per million and coupling constants (*J*) in hertz.

4.2. Typical procedure: acetylation of D-glucose

To a stirred suspension of D-glucose (1 mmol) in acetic anhydride (1 mL), was added $\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$ (2 mol %). The mixture was stirred at rt and the reaction was monitored using TLC. After 5 h, TLC (ethyl acetate/hexane, 1:1, v/v) showed the presence of only the pentaacetate. The reaction mixture was then diluted with dichloromethane, filtered to recover the $\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$, subsequently washed with dichloromethane. The combined filtrations were washed with saturated aqueous sodium carbonate solution and dried over anhydrous Na₂SO₄. The solvent was removed to give a clear colorless syrup which crystallized on drying under high vacuum (98% yield, nearly quantitative). ¹H NMR spectrum of this product showed it to be a mixture of α -D-glucopyranose pentaacetate with approximate 28% of the β -isomer.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.01.027.

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