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Sulfuric acid immobilized on silica: an efficient reusable catalyst for selective hydrolysis of the terminal *O*-isopropylidene group of sugar derivatives☆

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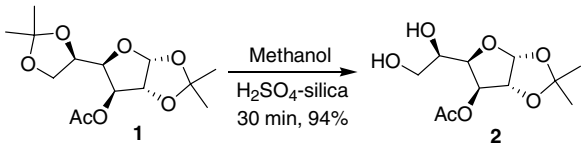
Dedicated to Professor Robert A. Field, Centre for Carbohydrate Chemistry, School of Chemical Sciences and Pharmacy, University of East Anglia, Norwich, UK

Abstract—Sulfuric acid immobilized on silica proved to be an efficient catalyst for selective hydrolysis of the terminal *O*-isopropylidene group of sugar derivatives. The method is very simple and economic for large-scale synthesis in which the catalyst is recovered and reused for several runs. Reactions with di-*O*-isopropylidene derivatives of D-glucose, D-mannose, D-fructose and L-sorbose led to the formation of the corresponding mono-*O*-isopropylidene derivatives in good to excellent yields.

Understanding the role of carbohydrates in biology is highly dependent on the development of the synthesis of oligosaccharides.[1] Thus, with the rise of glycobiology, simplifying protecting group manipulation strategy has become an important area of research. Selective protection and deprotection of functional groups is a major challenge for the total synthesis of various natural products including oligosaccharides. Isopropylidene derivatives have been widely used to protect 1,2- and 1,3-diols in carbohydrate and nucleoside chemistry. Deprotection of a terminal isopropylidene group in the presence of an inner one often becomes necessary in a synthetic scheme. Various protic acids such as aq HCl,[2] aq HBr,[3] 60% aq AcOH,[4] aq H_2SO_4,[5] trifluoroacetic acid[6] and Lewis acids such as $Zn(NO_3)_2{\cdot}6H_2O$,[7] $CuCl_2{\cdot}2H_2O$ in ethanol,[8] $CeCl_3{\cdot}7H_2O$ $(COOH)_2$[9] and $BiCl_3$[10] have been used for the deprotection of isopropylidene acetals. Dowex H^+ ion-exchange resin in methanol–water (9:1)[11] has also been used for the same purpose. However, some of the protic acids are strongly acidic, and often, non-selective hydrolysis of isopropylidene groups is observed in the presence of water in these reactions. Moreover, these reactions become incompatible with various acid labile protecting groups such as *p*-methoxybenzyl, TBDMS, etc. Interestingly, thiourea[12] has been used for the hydrolysis of *O*-isopropylidene groups and can be considered as neutral. Supported reagents such as $FeCl_3{\cdot}6H_2O$ on silica,[13] $NaHSO_4$ on silica[14] and $HClO_4$ on silica[15] have also been used for this important transformation. In spite of their potential, many of these methods suffer from the use of toxic materials, harsh reaction conditions, strong oxidizing conditions, long reaction times, large amounts of reagents, lower yields and incompatibility with various protecting groups. Therefore, a mild and general procedure for the hydrolysis of terminal *O*-isopropylidene groups, compatible with a range of protecting groups, would be useful.

Noting recent reports on the use of silica–sulfuric acid by Zolfigol and co-workers[16] for various organic transformations, we were drawn to explore the applicability of sulfuric acid immobilized on silica (H_2SO_4–silica) in the field of synthetic carbohydrate chemistry. In continuation of our efforts towards developing new reagent



Scheme 1. Hydrolysis of the terminal *O*-isopropylidene.

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Table 1. Synthesis of *O*-isopropylidene derivatives from free sugars using H_2SO_4–silica[a]

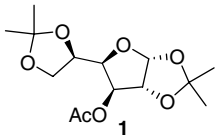
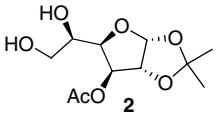
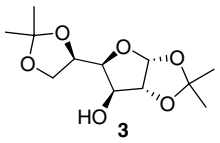
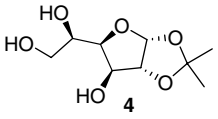
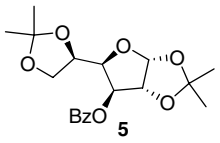
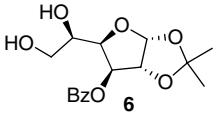
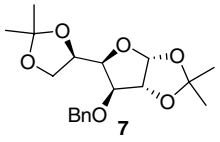
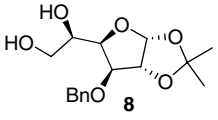
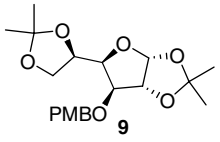
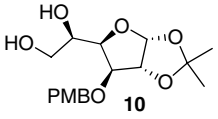
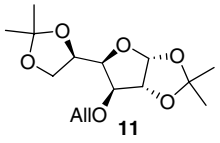
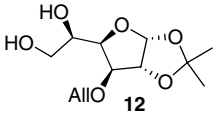
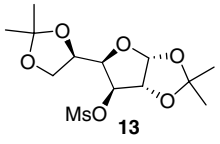
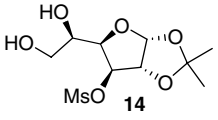
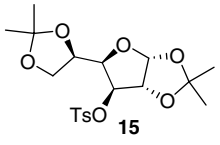
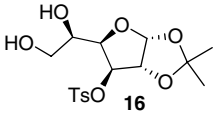
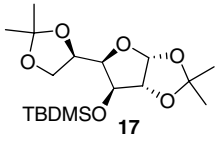
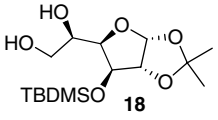
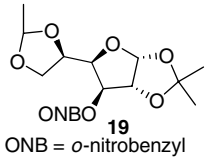
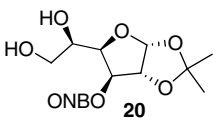
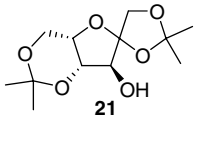
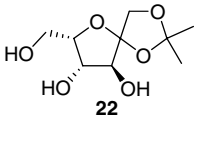
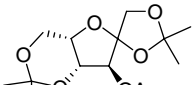
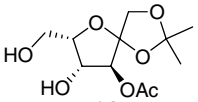
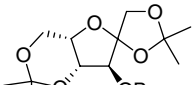
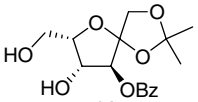
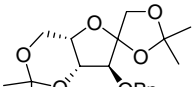
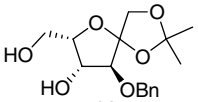
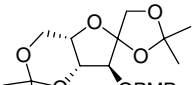
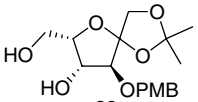
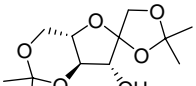
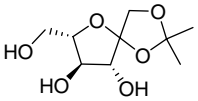
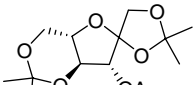
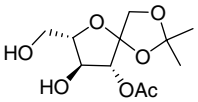
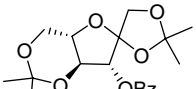
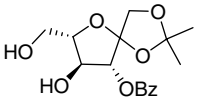
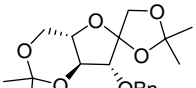
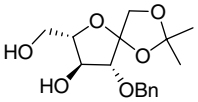
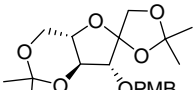
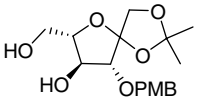
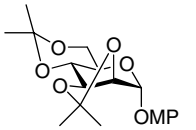
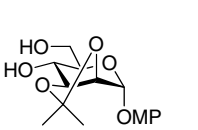
Entry	Starting material	Product	Time (min)	Yield (%)
Glucofuranose derivatives				
1	 **1**	 **2**	30	94
2	 **3**	 **4**	30	88
3	 **5**	 **6**	40	89
4	 **7**	 **8**	30	91
5	 **9**	 **10**	30	90
6	 **11**	 **12**	30	86
7	 **13**	 **14**	45	78
8	 **15**	 **16**	45	81
9	 **17**	 **18**	45	90
10	 **19** ONB = *o*-nitrobenzyl	 **20**	60	80
Sorbofuranose derivatives				
11	 **21**	 **22**	30	83

Table 1 (*continued*)

Entry	Starting material	Product	Time (min)	Yield (%)
12	 **23**	 **24**	30	89
13	 **25**	 **26**	40	87
14	 **27**	 **28**	30	90
15	 **29**	 **30**	30	91
Fructofuranose derivatives				
16	 **31**	 **32**	30	82
17	 **33**	 **34**	30	84
18	 **35**	 **36**	30	85
19	 **37**	 **38**	30	90
20	 **39**	 **40**	30	89
Mannopyranose derivatives				
21	 **41** MP = *p*-methoxyphenyl	 **42**	25	70

Data obtained for those compounds reported in the literature are in agreement with the literature data.
[a] All compounds gave satisfactory ^{1}H and ^{13}C NMR and mass spectra.

systems for various carbohydrate reactions we found that H_2SO_4–silica[17,18] could act as a good protic acid source under milder and safer conditions than other silica supported reagents such as $HClO_4$–silica. Extending its application to synthetic carbohydrate chemistry, we now report a very simple method for the hydrolysis of terminal *O*-isopropylidene groups in the presence of a series of protecting groups frequently used for oligosaccharide synthesis.

To start, 3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**, 1 mmol) was dissolved in commercial grade methanol (5 mL) and treated with H_2SO_4–silica[19] (100 mg) at room temperature. After 30 min, TLC showed complete conversion of the starting material to a slower running component.[20] The product obtained through filtration and evaporation of the solvent was confirmed as 3-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**2**) by NMR and mass spectrometric analysis. It is worth noting that the reaction was very sluggish in acetonitrile (~20% conversion after 24 h) and no reaction occurred in dichloromethane. A similar reaction with normal silica did not produce any of the desired products even after 3 days at room temperature. When the same transformation was carried out using aq AcOH, the commonly used method for the deprotection of terminal isopropylidene groups, it took 12 h for complete conversion of the starting material. This evidence affirms the potential of the method (Scheme 1).

Our next target was to ascertain the compatibility of this reagent system with various protecting groups including acid labile *p*-methoxybenzyl (PMB), *tert*-butyldimethylsilyl (TBDMS), *o*-nitrobenzyl (ONB) groups, etc. For this purpose, a set of di-*O*-isopropylidene glucofuranose derivatives having different protecting groups at 3-OH were prepared and subjected to the above reaction conditions. In all cases, satisfactory yields of the desired mono-*O*-isopropylidenes were obtained without affecting the protecting group at position 3. The results are summarized in Table 1.

To judge the applicability of the methodology for different sugar scaffolds, a series of di-*O*-isopropylidene derivatives of L-sorbofuranose and D-fructofuranose were prepared. Under similar conditions, they also gave the corresponding mono-*O*-isopropylidene derivatives in good to excellent yields. All compounds gave satisfactory ^1H and ^{13}C NMR spectra and mass spectra after filtration through a pad of Celite and evaporation of the solvent in vacuo.[21] Finally, the reaction of *p*-methoxyphenyl 2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranoside (**41**) under the same conditions afforded *p*-methoxyphenyl 2,3-*O*-isopropylidene-α-D-mannopyranoside (**42**) in 70% yield along with the completely deprotected *p*-methoxyphenyl α-D-mannopyranoside (~15%). Compound **42** was purified by chromatography. The reaction conditions did not affect the acid-labile *p*-methoxyphenyl glycoside. This reaction confirmed that the reagent system could be useful for other selective deprotections of *O*-isopropylidene groups.

In addition to the simplicity of the product isolation, the catalyst can be recycled several times. Over seven cycles, the catalyst did not show any significant change in reactivity. Moreover, reaction with compound **1** on 20 g scale showed no difference in the outcome confirming the applicability of the reagent system on a large-scale.

In conclusion, a simple work-up and purification-free method has been reported for deprotection of terminal *O*-isopropylidene groups using reusable H_2SO_4–silica which is equally applicable on large-scale. The time required for the desired transformations is remarkably shorter compared to the other methods available in the literature. It is expected that this cheap, environmentally friendly, safe and easy to handle reagent system will find applications in oligosaccharide synthesis. Compounds derived from these experiments are being used in our laboratory for the synthesis of furanoside-containing oligosaccharides.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.125.

References and notes

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19. *Preparation of H_2SO_4–silica*: To a slurry of silica gel (10 g, 200–400 mesh) in dry diethyl ether (50 mL) was added commercially available concd H_2SO_4 (3 mL) with shaking for 5 min. The solvent was evaporated under reduced pressure resulting in free flowing H_2SO_4–silica which was then dried at 110 °C for 3 h.
20. *General procedure*: To a solution of the starting material (1 mmol) in commercial grade MeOH (5 mL), H_2SO_4–silica (100 mg) was added and the mixture was stirred at room temperature for the required time (Table 1). After complete conversion, the mixture was filtered through a pad of Celite®, washed with CH_2Cl_2 (2 mL) and the filtrate was evaporated in vacuo. The compound thus obtained was sufficiently pure for further use (NMR and mass spectrometry). For the mannose derivative only, the crude product was purified by column chromatography using *n*-hexane–EtOAc (1:1).
21. Copies of selected ^1H and ^{13}C NMR spectra are available in the Supplementary data.