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

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Dedicated to Dr. Alan H. Haines, University of East Anglia, Norwich, UK

Abstract—Sulfuric acid immobilized on silica proved to be an efficient catalyst for the synthesis of *O*-isopropylidene sugar derivatives from reducing sugars. The method is very simple and economic for large-scale synthesis in which the catalyst is recovered and reused several times. Reactions with D-glucose, D-galactose, D-mannose, L-rhamnose, L-arabinose, D-xylose and L-sorbose led to the formation of the corresponding thermodynamically stable di-*O*- and/or mono-*O*-isopropylidene derivatives in good to excellent yields.

Formation of *O*-isopropylidene derivatives of aldoses and ketoses by condensation with acetone has been widely used in synthetic, structural and conformational studies.[1] Acetonides of sugars are important due to their pharmacological properties and utility as reaction intermediates for the synthesis of bioactive molecules. For example, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose is well known for its anti-inflammatory and antipyretic activities with very low toxicity,[2] and therefore has become commercially demanding as a starting material for a diverse range of bioactive molecules such as antibiotics, cytotoxic, anti-inflammatory and antipyretic agents. The corresponding di-*O*-isopropylidene derivative of L-sorbose has been used for the synthesis of vitamin C[3] and for the large-scale preparation of 1-deoxynojirimycin.[4] Other di- and/or mono-*O*-isopropylidene derivatives have also found wide applications in total syntheses of large macromolecules.

Several methods are available in the literature for the synthesis of *O*-isopropylidene derivatives of sugars. The conventional method consists of the condensation of a sugar diol with acetone in the presence of a suitable catalyst under anhydrous conditions. Catalysts used in these reactions include mineral acids,[5] anhydrous zinc chloride along with phosphoric acid,[6] ion exchange resins,[7] anhydrous copper(II) sulfate,[8] iodine,[9] anhydrous ferric chloride,[10] boron trifluoride etherate,[11] anhydrous aluminium chloride[12] and Zeolite HY.[13] However, many of these methods suffer from the use of toxic chemicals, low yields, very long reaction times and harsh reaction conditions. Moreover, in each case, extensive work-up and chromatographic purification become almost inevitable to achieve pure products. Hence, there is a clear need for a simple and practical methodology for the synthesis of this useful class of molecules on large scale.

Silica-supported reagents have gained much attention as alternative catalysts to develop stoichiometric and/or work-up free reaction methods in sugar chemistry.[14] Noting recent reports on the use of sulfuric acid immobilized on silica in various organic reactions,[15] including a one-pot acetalation–acetylation of glycosides[16] from our laboratory, we have extended its application. In this communication, we report a simple, work-up free method for the synthesis of *O*-isopropylidene derivatives from free sugars using sulfuric acid immobilized on silica as a catalyst.

When a mixture of commercially available D-glucose (**1**, 1 mmol) in dry acetone (5 mL) was stirred in the presence of H_2SO_4–silica[17] at room temperature, no change in the starting material was evident by TLC even after several hours. Next, the mixture was stirred under reflux

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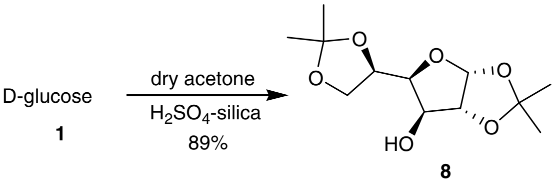


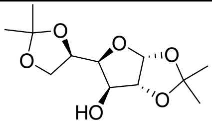
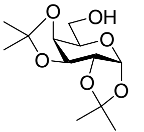
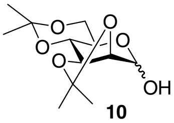
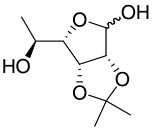
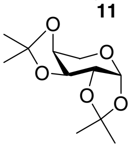
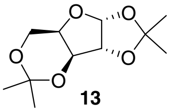
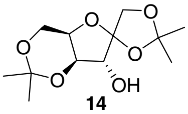
Scheme 1. Acetonation of D-glucose.

and the starting material was completely converted to a faster running component,[18] presumably 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside (**8**), within 3 h in 89% yield (Scheme 1). The compound collected after filtration through a pad of Celite® was proved to be >95% pure **8**[13] by NMR and mass spectrometry. Under the same conditions, D-galactose afforded 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**9**) in 78% yield. It is worth mentioning that in this case, when the reaction was started on a pre-heated oil-bath, only a pyranoside product was obtained but slow elevation of the temperature resulted in a mixture of furanoside and pyranoside in a 1:5 ratio. It was presumed that at the lower temperature, the kinetically controlled product was favoured. To increase the amount of furanoside derivative the reaction was conducted at 40 °C, but the ratio remained the same after 5 h and the yield dropped to ~30%.

D-Mannose, L-rhamnose and L-arabinose led to the formation of the corresponding pyranoside derivatives, exclusively, in 82%, 87% and 91% yields, respectively. D-Xylose and L-sorbose were converted to their di-*O*-isopropylidene furanoside derivatives under similar conditions. The results are summarized in Table 1. A 25 mmol scale acetonation reaction with D-glucose (**1**) gave the desired compound **8** without affecting the overall yield which suggests that this reagent system is equally viable on large scale. After filtration of the product, the H_2SO_4–silica was recovered and used again after drying. Reuse up to five times showed almost no change in the reactivity of the catalyst or the yield of the desired product.

In conclusion, a simple work-up and purification free method has been developed for the synthesis of di- and/or mono-*O*-isopropylidene derivatives from free sugars using reusable H_2SO_4–silica as the catalyst.

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

Entry	Starting material	Product[b]	Time (h)	Yield (%)	Ref.
1	D-glucose (**1**)	 **8**	3	89	13
2	D-galactose (**2**)	 **9**	3	78	13
3	D-mannose (**3**)	 **10**	3	82	19
4	L-rhamnose (**4**)	 **11**	2	87	20
5	L-arabinose (**5**)	 **12**	2	91	13
6	D-xylose (**6**)	 **13**	1.5	83	13
7	L-sorbose (**7**)	 **14**	2	86	13

[a] All reactions were started on a pre-heated oil bath so that reflux commenced immediately after addition of the catalyst.

[b] Analytical data for all products were consistent with known products from the literature.

The strategy is equally compatible to large-scale synthesis.

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra of compounds **8**, **9**, **10**, **11**, **12**, **13**, and **14** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.050.

References and notes

1. (a) Mills, J. A. *Adv. Carbohydr. Chem.* **1955**, *10*, 1–53; (b) De Belder, A. N. *Adv. Carbohydr. Chem.* **1965**, *20*, 219–302; (c) De Belder, A. N. *Adv. Carbohydr. Chem.* **1977**, *34*, 179–241.
2. Goi, A.; Bruzzese, T.; Notarianni, A. F.; Riva, M.; Ronchini, A. *Arzneim.-Forsch./Drug Res.* **1979**, *29*, 986–990.
3. Jenkins, R. O. In *Biotechnological Innovations in Chemical Synthesis*; Van Dam Mieras, R. C., Currell, B., Eds.; Elsevier, 1997.
4. Behling, J.; Farid, P.; Medich, J. R.; Scaros, M. G.; Prunier, M. *Synth. Commun.* **1991**, *21*, 1383–1386.
5. (a) Stevens, J. D. *Chem. Commun.* **1969**, 1140–1141; (b) Hughes, N. A.; Speakman, P. R. H. *Carbohydr. Res.* **1965**, *1*, 171–175.
6. Schmidt, O. Th. *Methods Carbohydr. Chem.* **1963**, *2*, 318–320.
7. (a) Nair, P. R. M.; Shah, P. M.; Sreenivasan, B. *Starch* **1981**, *33*, 384–387; (b) Nikiforov, V. A.; Zarutsski, V. V.; Chapanov, I. D.; Vasiléva, I. B.; Dolgushina, N. N. *Khim. -Farm. Zh.* **1982**, *16*, 1102–1103.
8. (a) Morgenlie, S. *Acta Chem. Scand.* **1973**, *27*, 3609–3610; (b) Morgenlie, S. *Acta Chem. Scand. Ser. B* **1975**, *29*, 367–372.
9. Kartha, K. P. R. *Tetrahedron Lett.* **1986**, *27*, 3415–3416.
10. Singh, P. P.; Gharia, M. M.; Dasgupta, F.; Srivastava, H. C. *Tetrahedron Lett.* **1977**, 439–440.
11. Pfaff, P. K.; Paust, J.; Hartmann, H. (BASF, A: -G.) Ger. Offen. DE 3, 505, 150 (cl. C07H9/04), 21 August 1986, Appl. 15 February 1985 (CA 106:18984r).
12. Lal, B.; Gidwani, R. M.; Rupp, R. H. *Synthesis* **1989**, 711–713.
13. Rauter, A. P.; Ramôa-Ribeiro, F.; Fernandes, A. C.; Figueiredo, J. A. *Tetrahedron* **1995**, *51*, 6529–6540.
14. For instance see: (a) Mukhopadhyay, B.; Maurer, S. V.; Rudolph, N.; van Well, R.; Russell, D. A.; Field, R. A. *J. Org. Chem.* **2005**, *70*, 9059–9062; (b) Mukhopadhyay, B.; Kartha, K. P. R.; Russell, D. A.; Field, R. A. *J. Org. Chem.* **2004**, *69*, 7758–7760; (c) Mukhopadhyay, B.; Russell, D. A.; Field, R. A. *Carbohydr. Res.* **2005**, *340*, 1075–1080; (d) Mukhopadhyay, B.; Collet, B.; Field, R. A. *Tetrahedron Lett.* **2005**, *46*, 5923–5925; (e) Chakraborti, A. K.; Gulhane, R. *Chem. Commun.* **2003**, 1896–1897; (f) Agarwal, A.; Rani, S.; Vankar, Y. D. *J. Org. Chem.* **2004**, *69*, 6137–6140; (g) Misra, A. K.; Tiwari, P.; Agnihotri, G. *Synthesis* **2005**, *2*, 260–266; (h) Iranpoor, N.; Firouzabadi, H.; Jamalian, A.; Kazemi, F. *Tetrahedron* **2005**, *61*, 5699–5704; (i) Iranpoor, N.; Firouzabadi, H.; Jamalian, A. *Synlett* **2005**, 1447–1449.
15. For instance see: (a) Zolfigol, M. A.; Bamoniri, A. *Synlett* **2002**, 1621–1623; (b) Zolfigol, M. A. *Tetrahedron* **2001**, *57*, 9509; (c) Zolfigol, M. A.; Shirini, F.; Ghorbani Choghamarani, A.; Mohammadpoor-Baltork, I. *Green Chem.* **2002**, *4*, 562; (d) Shirini, F.; Zolfigol, M. A.; Mohammadi, K. *Bull. Korean Chem. Soc.* **2004**, *25*, 325–327.
16. Mukhopadhyay, B. *Tetrahedron Lett.* **2006**, *47*, 4337.
17. *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 (1 mL) and the slurry shaken for 5 min. The solvent was evaporated under reduced pressure resulting in free flowing H_2SO_4–silica which was dried at 110 °C for 3 h and used for the reactions.
18. *General procedure*: To a slurry of the commercially available free sugar (1 mmol) in dry acetone (5 mL) was added H_2SO_4–silica (20 mg) and the mixture was refluxed for the required time (Table 1). Then the mixture was filtered through a pad of Celite®, washed with CH_2Cl_2 (5 mL) and evaporated to dryness. The resulting product was characterized by NMR spectroscopy and mass spectrometry.
19. Gelas, J. *Carbohydr. Res.* **1978**, *67*, 371–375.
20. Haines, A. H. *Carbohydr. Res.* **1965**, *1*, 214–217.