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H₂SO₄-SiO₂: Highly efficient and novel catalyst for the Ferrier-type glycosylation

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Dedicated to Professor Gengyuan Tian on the occasion of his 70th birthday.

Abstract

Sulfuric acid immobilized on silica gel is designed as a very useful catalyst for synthesis of 2,3-unsaturated glycopyranosides. This handy, metal-free, environment friendly transformation provides high yields and α -stereoselectivities in a very few amount (<0.02 eq.) of catalyst and in short reaction times (<10 min).

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Double bond rearrangements in carbohydrate systems lead to various kinds of sugar transformations [1]. In these products of transformations, 2,3-unsaturated-*O*-glycosides have received much attention in recent years, because they are very useful chiral building blocks in the synthesis of a great deal of compounds: oligosaccharides [2], glycopeptides [3], modified carbohydrates [4], nucleosides [5], and many bioactive natural products [6]. Besides, they are main building blocks for diversity-oriented pilot library realization [7]. Recently, Boysen *et al.* reported that the 2,3-unsaturated pyranoside could be converted into a new type of olefin phosphorus chelate ligand in asymmetric synthesis [8], which established the further importance. The method widely employed to obtain the 2,3-unsaturated glycosides is Lewis acid-catalyzed allylic rearrangement of glycals, which is well known as the Ferrier reaction [9]. Up till now, a variety of acids have been used for transformation such as BF₃·OEt₂ [9a], IDCP [10], TMSOTf [11], I₂ [12], Sc(OTf)₃ [13], InCl₃ [14], Yb(OTf)₃ [15], BiCl₃ [16], Dy(OTf)₃-immobilized in ionic liquids [17], ZnCl₂ [18], FeCl₃ [19], HClO₄-SiO₂ [20], NiCl₅ [21], Er(OTf)₃ [22], Fe₂(SO₄)₃·*x*H₂O [23] and ZnCl₂/Al₂O₃ [24]. Recently, H₂SO₄-SiO₂ as a silica-supported reagent [25] has attracted much attention for its easy preparation, low cost, high efficiency and environmental benignness. In addition, it has already been used in the area of sugar chemistry, *e.g.* acetalation–acetylation of sugars [26], synthesis of

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allylic,ethylene glycol monomethyl ether and cholesterol

Scheme 1. Synthesis of 2,3-unsaturated glycopyranosides catalyzed with sulfuric acid on silica gel.

 Table 1

 Glycosidation in different solvents and temperatures.

Entry	Solvent	Temperature (°C)	Time (min)	Yield (%) ^a
1	CH_2Cl_2	25	140	75
2	CH_2Cl_2	40	70	76
3	MeCN	25	160	36
4	MeCN	80	5	93

^a Isolated yields.

O-isopropylidene sugar derivatives [27], and glycosylation of free monosaccharides [28]. In this note, we wish to recommend H_2SO_4 -SiO₂ effectively catalyzed Ferrier reaction. Fortunately, the reaction used H_2SO_4 -SiO₂ as the catalyst obtained excellent yields and short reaction time (Scheme 1).

Firstly, the glycosidation of 3,4,6-tri-O-acetyl-D-glucal (20 mg) with benzyl alcohol catalyzed by H₂SO₄-SiO₂ (1.5 mg, 0.9 mmol H⁺/g) was served as the model reaction to optimize the desired solvent and temperature. The preliminary results, which were summed up in the Table 1, showed that glycosidation of 3,4,6-tri-O-acetyl-D-glucal with benzyl alcohol can obtain the best results at 80 °C in MeCN with respect to the yield and reaction time.

Secondly, we examined the influence of dosage of H_2SO_4 -SiO₂ on the preceding glycosidation, which was summarized in Table 2. When smaller amount of catalyst was used, the reaction precedes much slower (entry 1). On the other hand, although the transformation performed much faster while catalyzed by more catalyst, many by-products were observed in the reaction mixture (entry 3). The table showed that the best results were achieved when the reaction was processed with 0.02 eq. H_2SO_4 -SiO₂.

According to the optimized condition, this method was extended to other *O*-nucleophiles including primary, secondary, propargyl, allylic and complex alcohols, such as ethylene glycol monomethyl ether (Table 3, entry 13). All reactions took place in less than 10 min with high yields. Except Cholesterol poorly soluble in acetonitrile, which led to the yield of the product of D-glucal and cholesterol being low (73%). When the solvent was changed into dichloromethane, the yield obviously increased (85%) (Table 3, entry 14). In most cases, two anomers of 2,3-unsaturated products (α and β) were obtained; while the α anomer was the primary product, which were characterized by analysis of spectral data (IR, ¹H NMR and MS).

Table 2 Comparison of results of Ferrier transformation with different dosages H_2SO_4 -SiO₂ [32].

Entry	Dosage of catalysts (eq.) ^a	Time (min)	Yield (%) ^b
1	0.007	30	87
2	0.02	5	93
3	0.07	2	78

^a Corresponding to D-glucal.

^b Isolated yields.

In conclusion, we have introduced a highly efficient, convenient and environment friendly methodology to easily generate 2,3-unsaturated glycosides. In addition, the short reaction time, high yields, and sparing dosage (as less than 0.02 eq.) of catalyst inspired us to report this method. Furthermore, the reaction mixture does not need any workup; merely requires filtration to remove solid-support catalyst and purification by flash column chromatography. These features, combined with the fairly cheap catalyst, make this method an attractive alternative to existing methodologies for the preparation of 2,3-unsaturated glycosides.

Table 3 H_2SO_4 -SiO₂ catalyzed Ferrier transformation.

Entry	Acceptors	Products	Time (min)	Yield (%) ^a	α : β ratio ^b
1	PhCH ₂ OH	Aco Aco 2a	5	93	5:1 [22,33]
2	CH ₃ OH	Aco OccH ₃ 2b	5	88	4.4:1 [29]
3	CH ₃ CH ₂ OH	Aco CH ₂ CH ₃ 2c	5	100	5.2:1 [22]
4	CH ₃ CH ₂ CH ₂ OH	Aco Oc ₃ H ₇ -n 2d	10	92	4.5:1 [31]
5	CH ₃ (CH ₂) ₂ CH ₂ OH	Aco Orgenoration 2e	10	87	5.0:1 [22]
6	ОН	Aco Aco 2f	10	95	>19:1 [22]
7	OH	Aco Aco 2g	10	91	>19:1 [22]
8	(CH ₃) ₂ CHOH	Aco 2h	10	96	5.0:1 [22]
9	ОН	Aco 2i	10	96	10.0:1 [31]
10	СН ₃ СНСН ₂ СН ₃ I OH	Aco 2j	10	91	4.0:1 [19]
11	HO	Aco 2k	10	92	5.7:1 [31]
12	<i>n</i> -C ₈ H ₁₇ OH	Aco OK 8H17-n 21	10	88	2.5:1 [29]

Table 3 (Continued)

Entry	Acceptors	Products	Time (min)	Yield (%) ^a	α : β ratio ^b
13	H ₃ COCH ₂ CH ₂ OH	Aco	10	87	7.0:1 [30]
14	HO C8H17	Aco OChol 2n	40 (40°)	73 (85 [°])	>19:1 [16]

^a Isolated yields.

^b α : β ratios were based on the integration of the corresponding anomeric protons in the ¹H NMR (500 MHz) spectrum.

^c Dichloromethane as the solvent.

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- [32] Preparation of H_2SO_4 -SiO₂ catalyst: the silica gel (5 g, 200–300 mesh) was added in dry Et₂O (50 mL) and the mixture was stirred into a pulp. Then concd. H_2SO_4 (250 μ L) is added in the contents. After stirred 5 minutes, the solvent was evaporated, and the remains were dried at 120 °C for 3 h to gain the free flowing powder of H_2SO_4 -silica. The loading capacity of H_2SO_4 on silica gel is 0.9 mmol H⁺/g.
- [33] General procedure of Ferrier transformation. To a stirred solution of 3,4,6-tri-O-acetyl-D-glucal (0.074 mmol, 20 mg) and alcohols (0.11 mmol) in anhydrous MeCN 0.5 mL at 80 °C was added H₂SO₄-SiO₂ (1.5 mg). After completion of the reaction (monitored by TLC), the mixture was filtered, and rinsed with CH₂Cl₂ (2 mL). The solvent was evaporated under reduced pressure; and then the reaction product was purified by column chromatography (400 mesh silica) to afford pure corresponding 2,3-unsaturated glycoside. The structures of products were identified through comparison of these spectra data with those in the known literatures. The analytical data for all described compounds are available in the editorial office of CCL.