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Solid silica sulfuric acid (SSA) as a novel and efficient catalyst for acetylation of aldehydes and sugars

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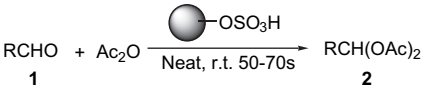
Abstract—Acetylation of aldehydes and sugars catalyzed by solid silica sulfuric acid (SSA) is described. In these reactions SSA shows a highly catalytic nature: easy to handle procedure, short reaction time, recycle exploitation, insensitivity to air and moisture, excellent isolated yields. The catalyst could be recycled at least five times.

1. Introduction

Protection of aldehydes is a frequently desired exercise in organic synthesis as it is often necessary to carry out a reaction on a multifunctional substrate without affecting a carbonyl group.[1] Previously, aldehydes are often protected by acetalization through reaction between aldehydes and alcohols[2] or trimethyl orthoformate[3] in the presence of acid catalyst or others such as copper(II) tetrafluoroborate,[4] DDQ–EtOH,[5] CAN–Na_2CO_3,[6] etc. However, these methods have some drawbacks such as long reaction time, high temperature, use of costly catalysts, use of additional reagents, requirement of special effort for catalyst preparation, need to use special apparatus, moderate yields, and side reactions. The most serious drawback is that these methods have no global utility and most of the products are liquid, which may contain impurities and are difficult to be purified compared to the powder and crystal.

Thus, 1,1-diacetates are developed as new protecting groups for aldehydes due to their stabilities, easy purification, and easy conversion into parent aldehydes.[7–11] Usually, they are obtained from aldehydes and acetic aldehyde using strong proton acids such as sulfuric acid,[12] phosphoric acid,[12] methanesulfonic acid[12] or Lewis acid as Nafion-H,[13] $ZnCl_2$,[14] ferric chloride,[11] phosphorus trichloride[15] or LiBr,[16] H_2NSO_3H.[17] These methods have not been entirely satisfactory owing to such drawbacks as low yields (4% in the case of 4-nitrobenzaldehyde[15]), long reaction time (up to 120 h in the case of 2-furaldehyde[15]), problems of corrosion, effluent pollution and non-recoverable catalysts and use of toxic organic solvents. In order to overcome these drawbacks, mild, quick, and environmentally friendly conditions have been developed. There are so many solid catalysts, such as β-zeolite,[18] sulfated zirconia,[19] montmorillonite clays,[20] expensive graphite,[21] trimethylchlorosilane/sodium iodide,[22] scandium triflate,[23] TiO_2/SO_4^{2-} solid superacid,[24] iodine,[25] $Bi(OTf)_3xH_2O$,[26] $AlPW_{12}O_{40}$,[27] and LiOTf.[28]

We herein disclose a new mild and efficient protocol (Scheme 1) for diacetylation of aldehydes using Ac_2O (3–20 equiv) catalyzed by 0.06 mol % of SSA in short time.



Scheme 1.

Carbohydrates, which are central to a wide array of biological processes,[29] have received much attention. Based on the concept of protected and unprotected glycosylation reagents, further extension to so-called 'programmable' syntheses[30] need efficient synthesis of fast and convenient protected sugar building blocks for the synthesis of biologically potent oligosaccharides, glycoconjugates, as well as natural products.[31] Per-O-acetylation is a frequently used reaction for protection of sugars and is often carried out using acetic anhydride as reagent and a catalyst such as pyridine,[32] pyridine derivatives,[33] sodium acetates.[34] However, dealing with large volumes of pyridine and other homogeneous catalysts is troublesome and recovery of catalysts is also difficult. A variety of other catalysts, iodine,[35] strong inorganic

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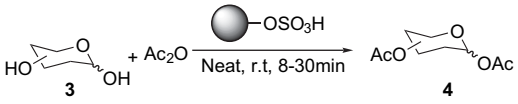
acid,[36] Lewis acid,[37] anionic surfactants,[38] montmorillonite K10,[39] Nafion-H,[40] H-β zeolite,[41] zirconyl sulfophenyl phosphonate,[42] lipases,[43] $Cu(OTf)_2$,[44] and $Sc(OTf)_3$[45] have been investigated.

SSA is an excellent acidic catalyst, which was frequently used to promote some important reaction.[46–48] But it is never used to catalyze acetylation reactions. Herein, we report a new mild and efficient protocol (Scheme 2) for acetylating sugar with Ac_2O catalyzed by SSA at room temperature.



Scheme 2.

2. Results and discussion

As shown in Table 1, a series of geminal diacetates **2** were synthesized with the catalyst SSA at room temperature. We found that both aromatic and aliphatic aldehydes gave high yields (≥80%) and the reaction time was shorter than that of previous methods. The results indicated that the nature of substituents on the aromatic ring had no effect on the reaction, except 2-methoxybenzaldehyde, which gave lower yield due to the steric hindrance effect. Ketones, for example, acetophenone and cyclohexanone could not be converted into the corresponding geminal diacetates even when the reaction complexes were stirred for 24 h.

The results in Table 2 indicate that in contrast to the conventional **4**, wherein an excessive amount of Ac_2O was needed and neutralization followed by tedious workup and purification, our method employing stoichiometric amount of Ac_2O offers a chance to carry out the **4** under solvent-free conditions. Disaccharides (entries **3f–3g**) required longer reaction time than pentoses and hexoses (entries **3a–3e**) and the amount of SSA for disaccharides was 0.06 mol %, while it was 0.03 mol % for monosaccharides. The reaction terminal could easily be monitored when the reaction system cooled to room temperature automatically due to its heat liberation. It could also be judged by TLC. The outstanding feature of this method was that the catalyst could be easy recycled five times without significant deactivation. A comparison of this method with previous ones, in Table 3, clearly shows the advantages of this method. The data in Table 3 also show that some protocols took much longer time, some used no-recovery catalyst, or some used dangerous materials with reduced isolated yields. This protocol is so efficient in acetylation of 3-nitrobenzaldehyde in less than 0.8 min, while the same transformation requires 0.5–12 h if $FeCl_3$,[11] β-zeolite,[18] and LiOTf[28] are used. The use of LiOTf is equally effective for benzaldehyde, but reaction time is much longer (14 h). Compared with K-10, which has shown no effect for 4-hydroxybenzaldehyde, the catalytic activity of SSA is observed in 99% yield and in a very short time (70 s).

Table 1. SSA-catalyzed solvent-free acetylation of aldehydes with acetic anhydride

Entry	Aldehyde	Ac_2O (equiv)	Time (s)	Yield[a,b] (%)	Mp (°C) found	Reported
1a	Butyraldehyde	3	60	91		
1b	Pentanal	3	60	85		
1c	Benzaldehyde	3	60	82	44–45	44–45[25]
1d	*p*-Nitrobenzaldehyde	20	50	99	124–125	125–126[20]
1e	*m*-Nitrobenzaldehyde	20	50	93	64–65	64–65[20]
1f	4-Chlorobenzaldehyde	15	50	99	81–82	81–82[25]
1g	2,4-Dichlorobenzaldehyde	20	50	85	102–104	101–102[17]
1h	4-Hydroxybenzaldehyde	15	70	99	92–93	
1i	*p*-Tolualdehyde	3	50	99	80–81	81–82[17]
1j	4-Cyanobenzaldehyde	15	50	98	101–102	98–102[9]
1k	4-Methoxybenzaldehyde	3	50	95	67–68	67–68[25]
1l	2-Bromobenzaldehyde	3	60	98	89–90	
1m	4-Bromobenzaldehyde	15	60	96	90–91	
1n	Salicylaldehyde	3	60	96	101–103	103–104[17]
1o	2-Methoxybenzaldehyde	3	50	80	66–68	

[a] Yield of pure isolated products.
[b] Products characterized by ^1H NMR spectroscopy and compared with authentic samples.

Table 2. SSA-catalyzed solvent-free per-O-acetylation of sugar with acetic anhydride[a]

Entry	Sugar	Product	Ac_2O (equiv)	Time (min)	α:β	Yield (%)
3a	D-Glucose	D-Glucopyranose pentaacetate	5.1	20	1.7	94[b]
3b	D-Xylose	D-Xylopyranose tetraacetate	4.1	10	20	96[b]
3c	D-Galactose	D-Galactopyranose pentaacetate	5.1	10	2.1	98[b]
3d	D-Mannose	D-Mannopyranose pentaacetate	5.1	20	4.2	89[b]
3e	L-Rhamnose	L-Rhamnopyranose tetraacetate	4.1	8	14	90[b]
3f	D-Lactose	D-Lactose octaacetate	9.0	25	1.9	91[c]
3g	D-Maltose	D-Maltose octaacetate	9.0	25	1.1	88[c]
3h	Sucrose	Sucrose octaacetate	9.0	30	20	91[c]

[a] Yield of pure isolated products.
[b] SSA 0.03 mol %.
[c] SSA 0.06 mol %.

Table 3. Comparison of protocols for acylation of aldehydes and sugars

Entry	Substrate	Catalyst	T (°C)	Time (min)	Yield (%)	Ref.
3a	D-Galactose	SSA	25	10	98	[a]
		I_2[c]	25	120	98	35b
		K-10[b]	25	600	92	39
		$Cu(OTf)_2$[b]	0→15	1500	90	44
		$Sc(OTf)_3$[b]	25	510	88	45
1b	3-Nitrobenzaldehyde	SSA	25	0.8		[a]
		$FeCl_3$	0	30	93	9
		β-Zeolite[e]	60	120	91	18
		LiOTf[b]	25	720	93	28
1c	4-Methoxybenzaldehyde	SSA	25	0.8	95	[a]
		LiOTf[b]	25	1740	91	28
1d	4-Hydroxybenzaldehyde	SSA	25	1.2	99	[a]
		K-10[d]	25			20

[a] Present work.
[b] Long reaction time.
[c] No recovery of catalyst.
[d] No reaction.
[e] Heat is needed.

In conclusion, SSA is a cheap, green, easily recycled, and efficient catalyst for acetylation of aldehydes and sugar at excellent yield. We believe that this method should be given a wide application in protection of the hydroxyl and carboxy.

3. Experimental

3.1. General

Melting points were measured with a Fisher–Johns melting point apparatus without correction. The nuclear magnetic resonance spectra were measured on a Bruker AM-400 spectrometer with Me_4Si (TMS) as the internal reference and $CDCl_3$ as solvent.

3.2. General procedure for acetylation of aldehydes

Aldehyde (1 mmol), acetic anhydride (3–20 mmol), and SSA (0.06 mol %) were added in a flask and then stirred for about 1 min. The reaction was monitored by TLC. On completion $NaHCO_{3(aq)}$ and CH_2Cl_2 were added to the reaction system yielding three layers: water on the top, silica sulfuric acid in the middle, and CH_2Cl_2 at the bottom. The bottom layer was separated, washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated to crude product and subjected to flash column chromatography.

3.3. General procedure for per-O-acetylation of sugar

To a mixture of sugar (2 mmol) and acetic anhydride (4.1–9 mmol), SSA (0.03–0.06 mmol %) was added at room temperature, and the reaction system was stirred until the starting material disappeared completely (as monitored by TLC).

The workup procedure was as described above.

3.4. Preparation and recycle of SSA

The preparation of SSA was according to Mohammad Ali Zolfigol.[49] The middle layer in the first stage of the above work up procedure was separated. The residue was washed with 95% EtOH and dried at 110 °C for 12 h to give pure SSA for further use.

3.4.1. Spectral data of new products.

3.4.1.1. 4-Hydroxybenzaldehyde. Colorless crystal; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.54 (d, J=8.4 Hz, 2H), 7.13 (d, J=8.4 Hz, 2H), 2.31 (s, 3H), 2.12 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.95, 168.42, 151.29, 132.79, 127.80, 121.54, 88.85, 20.83, 20.57. Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.59; H, 5.41%.

3.4.1.2. 4-Bromobenzaldehyde. Colorless crystal; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.54 (d, J=8.4 Hz, 2H), 7.39 (d, J=8.0 Hz, 2H), 2.13 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.38, 134.23, 131.54, 128.14, 123.69, 88.85, 20.53. Anal. Calcd for $C_{11}H_{11}BrO_4$: C, 46.02; H, 3.86. Found: C, 46.15; H, 3.96%.

3.4.1.3. 2-Bromobenzaldehyde. Colorless crystal; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.62 (dd, J=8.4 Hz, J=1.2 Hz, 1H), 7.57 (dd, J=8.4 Hz, J=1.6 Hz, 1H), 7.30 (m, 2H), 2.13 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.08, 134.58, 132.94, 130.78, 127.58, 127.32, 122.24, 88.77, 20.41. Anal. Calcd for $C_{11}H_{11}BrO_4$: C, 46.02; H, 3.86. Found: C, 46.11; H, 3.85%.

3.4.1.4. 2-Methoxybenzaldehyde. Colorless crystal; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.49 (d, J=8.4 Hz, 2H), 7.36 (t, J=7.6 Hz, 1H), 7.00 (t, J=7.6 Hz, 1H), 6.91 (d, J=8.4 Hz, 1H), 3.83 (s, 3H), 2.11 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.31, 156.71, 130.65, 128.68, 123.54, 120.19, 110.69, 85.38, 55.36, 20.60. Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.54; H, 5.96%.

3.4.1.5. Sucrose. Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.62 (d, J=4 Hz, 1H), 5.35 (m, 3H), 5.01 (t, J=9.6 Hz, 1H), 4.82 (d, J=8 Hz, 1H), 2.11–1.95 (m, 26H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.30, 170.11, 169.73, 169.69, 169.65, 169.52, 169.26, 169.14, 103.60, 89.52, 78.71, 77.22, 76.58, 75.30, 74.60, 69.84, 69.20, 68.07, 67.78, 63.23, 62.44, 61.37, 20.26, 20.23, 20.18, 20.15, 20.12, 20.10. Anal. Calcd for $C_{29}H_{40}O_{19}$: C, 50.29; H, 5.82. Found: C, 50.36; H, 5.91%.

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