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An efficient method for the synthesis of acylals from aldehydes using silica-supported perchloric acid ($HClO_4$–SiO_2)

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Abstract—The synthesis of acylals from structurally diverse aldehydes has been performed in excellent yields under solvent-free conditions using $HClO_4$–SiO_2 as a mild, convenient, reusable, and heterogeneous catalyst. The procedure is operationally simple, environmentally benign and has the advantage of enhanced atom utilization. Furthermore, the catalyst can be recovered simply and reused efficiently a number of times without appreciable loss of activity.

Acylals are important starting materials in organic synthesis, especially for the preparation of dienes[1] and chiral allylic esters[2] and also act as cross linking reagents for cellulose in cotton.[3] They are among the most popular protecting groups for carbonyl compounds due to their stability under neutral and mild conditions.[4] Hence, methods for their synthesis have received considerable attention. Usually, they are prepared from aldehydes and acetic anhydride using strong protic acids such as sulfuric,[5a] methanesulfonic,[5b] phosphoric[5c] or perchloric acid,[5d] although the yields in many cases are poor. Lewis acids such as PCl_3,[6a] $ZnCl_2$,[6b] TMSCl–NaI,[6c] I_2,[6d] $FeCl_3$,[6e] NBS,[6f] anhydrous ferrous sulfate,[6g] LiBr,[6h] $InCl_3$,[6i] WCl_6,[6j] CAN,[6k] $LiBF_4$[6l] as well as some heterogeneous catalysts like clay,[7a,b] zeolites,[7c–e] Nafion-H,[7f] expansive graphite,[7g] and supported reagents[7h–j] are also used. However, these procedures are often accompanied by low product yields, longer reaction times, corrosive reagents, high catalyst loading, and stringent conditions. Recently, other methods employing catalysts such as $ZrCl_4$,[8] $Zn(BF_4)_2$,[9] $Fe_2(SO_4)_3{\cdot}xH_2O$,[10] $Bi(NO_3)_3{\cdot}5H_2O$,[11] $AlPW_{12}O_{40}$,[12] $H_6P_2W_{18}O_{62}{\cdot}24H_2O$,[13] and triflates such as $Sc(OTf)_3$,[14] $Cu(OTf)_2$,[15] $Bi(OTf)_3$,[16] and LiOTf[17] have been reported for this conversion. However, the former catalysts are required in large amounts whereas the latter triflates are costly, moisture sensitive and special efforts are required for their preparation. More recently, $Cu(BF_4)_2$[18] and $InBr_3$[19] have been introduced for this reaction. Though there are a number of procedures for the synthesis of acylals, these frequently require the use of an excess (1.5–8 equiv) of acetic anhydride and result in the generation of significant quantities of waste. Also, many of these methods require the use of potentially polluting solvents and high temperature. Consequently, a methodology is required that is mild, efficient, environmentally benign, site selective and has the advantage of enhanced atom economy.

Solid supported reagents are unique catalysts that have become popular over the last two decades.[20] The high catalytic activity, low toxicity, moisture, and air tolerance, their recyclability and particularly low price make the use of solid supported reagents attractive alternatives to conventional Lewis acids and triflates.[21] Although the catalytic applications of solid supported reagents for organic synthesis have been well established, relatively few examples are reported on the use of $HClO_4$–SiO_2.[22] Herein, we report $HClO_4$–SiO_2 (0.1 mol %) as a reusable catalyst for the synthesis of acylals from structurally diverse aldehydes with acetic anhydride under solvent-free conditions (Scheme 1).

Keywords: Acylals; Carbonyl compounds; Chemoselective; $HClO_4$–SiO_2; Protection.

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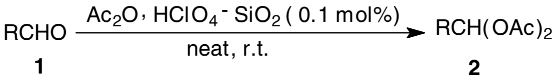


Scheme 1.

Initially, a systematic study was carried out for catalytic evaluation of silica-supported perchloric acid. When a mixture of benzaldehyde and acetic anhydride was stirred in the presence of 0.01 mol % $HClO_4$–SiO_2 at room temperature, the corresponding acylal was obtained in 70% yield in 30 min. Increasing the quantity of the catalyst to 0.05 and 0.1 mol % gave the corresponding product in 87% and 99% yields in 10 and 2 min, respectively. Use of just 0.1 mol % was sufficient to drive the reaction forward; larger amounts of the catalyst did not improve the results.

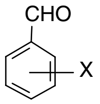
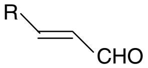
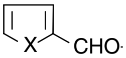
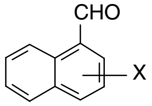
Next, the conversion of benzaldehyde to the corresponding diacetate was carried out at room temperature in the presence of $HClO_4$–SiO_2 (0.1 mol %) using various solvents such as chloroform (40%), dichloromethane (45%), acetonitrile (60%), and tetrahydrofuran (42%). However, the best yield of product (99%) was obtained under solvent-free conditions. The reusability of $HClO_4$–SiO_2 was examined with benzaldehyde as a model substrate and the results are presented in the experimental procedure.

The results summarized in Table 1 demonstrate the generality and scope of $HClO_4$–SiO_2 during the acylation of structurally diverse aldehydes. The electronic effects and the nature of the substituents on the aromatic ring did not show strongly obvious effects in terms of yields under the present reaction conditions. Various functional groups were tolerated under the present conditions, for example, Me, Cl, OMe, NO_2, F, and Br. Acid sensitive substrates like furfural (entry 4a) and thiophene aldehyde (entry 4b) gave the corresponding 1,1-diacetates in excellent yields without any side reactions, which are normally encountered under acidic conditions. The conjugated aldehydes (entries 3a–b) were diacetylated smoothly without any isomerization. Also, the reaction conditions tolerate moieties such as *O*-allyl (entry 2i), *O*-*p*-nitrobenzyl (entry 2j), *O*-*p*-*t*-butyl-dimethylsilyl (entry 2k), methylenedioxy (entry 2l), and OPh (entry 2m) which often undergo cleavage in strongly acidic media. In almost all cases, the reactions were quicker than those of the recently reported methods and the yields were very high.

While comparing the effect of catalysts in the acylation of 4-nitrobenzaldehyde, we found that $HClO_4$–SiO_2 was more effective than the recently reported catalysts in terms of the amount of acetic anhydride used, catalyst, yields and reaction times (Table 2).

Since ketones undergo acylation considerably more slower than aldehydes, it seemed plausible that our system could promote the chemoselective protection of aldehydes in the presence of ketones. Indeed, in the case of acetylbenzaldehyde the aldehyde group was converted to the corresponding diacetate while the ketone functionality remained unaffected (Scheme 2).

Table 1. $HClO_4$–SiO_2 catalyzed synthesis of 1,1-diacetates

Entry	Aldehyde	Time (min)	Yield[a,b] (%)
1	RCHO		
	a. R = CH_3	1	97
	b. R = $CH_3(CH_2)_2$	1	96
	c. R = $CH_3(CH_2)_5$	1	97
	d. R = $CH_3(CH_2)_7$	2	98
	e. R = CCl_3	4	94
2			
	a. X = H	2	99
	b. X = 4-CH_3	2	98
	c. X = 4-Cl	2	97
	d. X = 3-OMe	2	97
	e. X = 4-NO_2	2	99
	f. X = 4-Br	2	96
	g. x = 4-F	3	95
	h. X = 2-Cl, 3,4-$(OMe)_2$	5	96
	i. X = 3-*O*-allyl	3	96
	j. x = 3-*O*-PNB	5	95
	k. X = 4-*O*-TBDMS	4	95
	l. X = 3,4-(OCH_2O)	3	97
	m. X = 4-OPh	4	94
3			
	a. R = Ph (*E*)	15	96
	b. R = Me (*E*)	2	93
4			
	a. X = O	10	96
	b. X = S	10	95
5			
	a. X = H	10	93
	b. X = 2-OMe	30	90

[a] Yields of pure isolated product.

[b] All the products were characterized by IR, ^1H NMR, and mass spectroscopy.

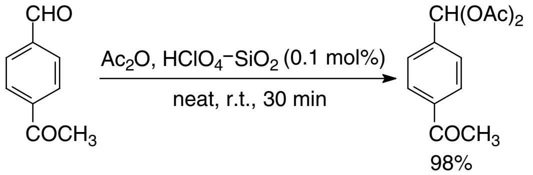
In order to generalize the catalytic efficiency of $HClO_4$–SiO_2 for other acylating agents, we employed benzaldehyde as a representative example during the reaction with different acid anhydrides (Table 3). Acylation with propionic, butyric, and *iso*-butyric anhydrides resulted in 88–93% yields of the geminal dicarboxylates.

In summary, it can be concluded that $HClO_4$–SiO_2 is an efficient and excellent catalyst for the synthesis of acylals in high yields under solvent-free and mild conditions in short reaction times. It has been reported that perchlorates can give rise to explosive reactions when heated at high temperatures in the presence of combustible compounds.[23] Therefore, the potential hazard connected with their manufacture and use has prevented their extensive application in industrial processes,[24] especially when large amounts of these compounds are involved. However, studies on the use of perchlorates in synthesis

Table 2. Comparison of the catalytic efficiency of $HClO_4$–SiO_2 against other reported catalysts for the conversion of 4-nitrobenzaldehyde (1 equiv) into the corresponding 1,1-diacetate

Catalyst	Amount of Ac_2O	Catalyst (mol %)	Temp (°C)	Solvent	Time (min/[h])	Yield[a] (%)
CAN	2 equiv	10	rt	None	[24]	96[6k]
NBS	1 mL	10	rt	None	[8]	98[6f]
$InCl_3$	2 equiv	10	rt	H_2O	[4]	88[6i]
$LiBF_4$	2 equiv	10	60	None	[23]	90[6l]
$ZrCl_4$	3 equiv	5	rt	None	30	92[8]
LiOTf	5–8 equiv	20	rt	None	[15]	94[17]
$Cu(OTf)_2$	3 equiv	2.5	rt	CH_2Cl_2	[4]	94[15]
$Sc(OTf)_2$	1.5 equiv	2	rt	$MeNO_2$	10	99[14]
$Cu(BF_4)_2 \cdot xH_2O$	1.5 equiv	1	rt	None	3	92[18]
$H_6P_2W_{18}O_{62} \cdot 24H_2O$	1 mL	1	rt	None	30	92[13]
$InBr_3$	3 equiv	0.1	rt	None	15	99[19]
$HClO_4$–SiO_2	1 equiv	0.1	rt	None	2	99

[a] Yields refer to pure isolated product.



Scheme 2.

Table 3. Conversion of benzaldehyde into geminal dicarboxylates with acid anhydrides

Aldehyde	Anhydride $(RCO)_2O$	Time (min)	Yield[a] (%)
PhCHO	$R = C_3H_7$	40	93
PhCHO	$R = i\text{-}C_3H_7$	50	90
PhCHO	$R = i\text{-}C_4H_9$	55	88

[a] Yields of pure isolated products.

have mainly been focused on the lithium salt, since it is highly soluble in ethereal solvents. As mentioned above, this compound is generally active when employed in stoichiometric or sub-stoichiometric amounts. In several cases, a large excess with respect to the reagent is required.[25] In the present work, solid-supported perchloric acid has been used with a very low loading (0.001 mmol, 0.1 mol %) at room temperature. This demonstrates that it is a very powerful promoter and this fact raises the question of its potential for use in industry.

1. Preparation of the catalyst

$HClO_4$ (1.25 g, 12.5 mmol, as a 70% aqueous solution) was added to a suspension of silica gel (23.75 g, 230–400 mesh) in diethyl ether (75 mL). The mixture was concentrated and the residue dried under vacuum at 100 °C for 72 h to afford $HClO_4$–SiO_2 (0.5 mmol g^{-1}) as a free flowing powder.

2. Typical procedure

A mixture of benzaldehyde (530.60 mg, 5 mmol) and freshly distilled Ac_2O (510.45 mg, 5 mmol) was stirred at room temperature in the presence of a catalytic amount of $HClO_4$–SiO_2 (10 mg, 0.005 mmol) for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with ethyl acetate (5 mL) and the catalyst was allowed to settle. The supernatant ethyl acetate layer was decanted off, the catalyst washed with ethyl acetate (2 mL) and the combined ethyl acetate layers were concentrated under reduced pressure to afford almost pure product, which was further purified by recrystallization from EtOAc–hexane (1:9) to give pure acetoxyphenylmethyl acetate (99%), identical by mp, IR, ^1H NMR and EIMS with an authentic sample. The recovered catalyst was activated by heating at 80 °C under vacuum for 2 h and reused for the acylation of fresh benzaldehyde (5 mmol), affording a 96% yield of acetoxyphenylmethyl acetate after 10 min. The recovered catalyst, after activation, was reused for four more consecutive acylations of benzaldehyde (5 mmol) affording 93%, 90%, 88%, and 85% yields, respectively, in 10, 12, 12, and 15 min.

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