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P_2O_5/Al_2O_3 as an efficient heterogeneous catalyst for chemoselective synthesis of 1,1-diacetates under solvent-free conditions

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Abstract—An efficient and chemoselective method for the preparation of acylals from different aldehydes using P_2O_5/Al_2O_3 and acetic anhydride under solvent-free conditions.
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Selective protection and deprotection of carbonyl groups are extremely important steps in modern organic chemistry.[1] 1,1-Diacetates (acylals) are one of the essential carbonyl protecting groups due to their stability under both neutral and basic media as well as under acidic conditions.[2] The diacetates of α,β-unsaturated aldehydes are important starting materials for Diels–Alder reactions and also are useful intermediates in industries.[3,4] Moreover, the acylal functionality can be converted into other functional groups by reaction with appropriate nucleophiles.[5,6] Some of the reported methods for the preparation of 1,1-diacetates from aldehydes and acetic anhydride include using sulfuric acid,[7] triflic acid,[8] PCl_3,[9] I_2,[10] $FeCl_3$,[2,11] NBS,[12] $Sc(OTf)_3$,[13] $Cu(OTf)_2$,[14] $Bi(OTf)_3$,[15] CAN,[16] $AlPW_{12}O_{40}$,[17] β-zeolite,[18] $LiBF_4$,[19] Zn–montmorillonite,[20] $In(OTf)_3$,[21] H_2NSO_3H,[22] $ZrCl_4$,[23] $Bi(NO_3)_3{\cdot}5H_2O$,[24] Wells–Dawson acid ($H_6P_2W_{18}O_{62}{\cdot}24H_2O$)[25] and silica sulfuric acid.[26] Although some of these methods have convenient protocols with good to high yields, the majority of these methods suffer at least from one of the following disadvantages: reaction under oxidizing conditions, using strong acid, high temperature, long reaction times, moisture sensitivity of the used reagent, high cost and high toxicity.

Recently, the use of catalysts and reagents supported on solid supports and solvent-free conditions was developed because such reagents not only cause to simplify the purification processes but also help to prevent the releasing of toxic reaction residues into the environment.[27] This has led to growth in the field of solid supported on alumina.[28] Although there are many reports using phosphorus pentoxide as a reagent in organic reactions,[29] P_2O_5 is difficult to handle due to moisture sensitivity at room temperature. However the preparation of P_2O_5 on alumina (P_2O_5/Al_2O_3) is straightforward and handling of the reagent is also easy. In addition this reagent could be removed from the reaction mixture by simple filtration.[30a] In continuation of over reports using P_2O_5[31] and reaction under solvent-free conditions,[32] herein we wish to report an extremely convenient, mild and highly chemoselective procedure for the conversion of aldehydes to the corresponding acylals in the presence of acetic anhydride and catalytic amount of P_2O_5/Al_2O_3. The reaction is easily carried out at room temperature under solvent-free conditions (Scheme 1).

$$\text{R-CHO} + \text{Ac}_2\text{O} \xrightarrow[\text{Neat, R.T.}]{P_2O_5\,/\,Al_2O_3} \text{R-CH(OAc)}_2$$

R= aryl, alkyl

Scheme 1.

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To optimize the reaction conditions, initially we tried to convert benzaldehyde (2 mmol) to its corresponding acylal with P_2O_5/Al_2O_3 (0.1 g, 15 mol %) and acetic anhydride (5 mmol, 0.48 mL) in various solvents and also under solvent-free conditions. As shown in Table 1, in comparison to conventional methods in solvent the yield of the reaction under solvent-free conditions is higher and the reaction time is shorter. Therefore, we employed the above conditions for the conversion of various aldehydes to the corresponding acylals under solvent-free conditions (Table 2).

As shown in Table 2 by using this catalyst, various aldehydes were converted to their corresponding diacetates in good to high yields and short reaction times (Table 2).[33] Aliphatics and α,β-unsaturated aldehydes produced acylals in good yields (Table 2, entries 19–22). The acid sensitive substrate (furfural) is converted to 1,1-diacetate in 83% yields without the formation of any side products (Table 2, entry 18). 4-(Dimethylamino)benzaldehyde failed to give 1,1-diacetate under the same conditions which may be due to the electron-donating property of dimethylamino group (Table 2, entry 23).[22] We investigated the reaction of 2-hydroxybenzaldehyde, 4-hydroxybenzaldehyde and vanillin under the above conditions and observed that both carbonyl and phenolic –OH groups were acylated (Table 2, entries 15–17).

Table 1. Conversion of benzaldehyde to its corresponding diacetate in different solvents and under solvent-free conditions in the presence of P_2O_5/Al_2O_3

Entry	Solvent[a]	Yield[c] (%)	Time (min)
1	Dichloromethane	72	60
2	Acetonitrile	78	60
3	Ethylacetate	50	120
4	Diethylether	55	120
5	Cyclohexane	60	120
6	Solvent-free[b]	86	45

[a] The reaction was carried out in 5 mL of solvents at rt.

[b] The reaction was carried out with 5 mmol of Ac_2O at rt.

[c] The yields refer to isolated pure products.

To evaluate the role of Al_2O_3, we tried the acylation of benzaldehyde, 4-nitrobenzaldehyde, 4-methoxy benzaldehyde and 3-phenylpropionaldehyde in the absence of Al_2O_3 and using P_2O_5. We found that the yields of acylals by using the combination of P_2O_5/Al_2O_3 were greater (average, 15%) than those with P_2O_5 alone. The effect of Al_2O_3 may be due to good dispersion of P_2O_5 on the surface of alumina leading to significant improvements in reactivity. Also Al_2O_3 as a supporter may minimize cross contamination between inorganic and organic components.[30]

Finally, to evaluate the selectivity of this method, we did investigate competitive reactions for acylation of aldehydes in the presence of ketones using P_2O_5/Al_2O_3 as catalyst.[34] With this catalytic system the highly selective conversion of aldehydes in the presence of ketones was observed (Table 3, entries 1–3). We also compared the acylation of benzaldehyde versus different acetals, these reactions proceeded with high selectivity in the presence of this catalyst so that under these conditions acetals were intact (Table 3, entries 4 and 5).

Table 2. Preparation of acylals in the presence of P_2O_5/Al_2O_3 under solvent-free conditions at room temperature[a,b]

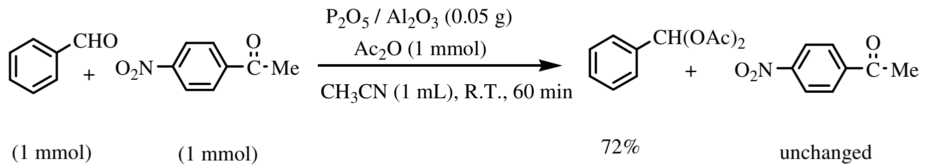
Entry	Substrate	Time (min)	Yield (%)	Mp (°C) or bp (°C) (mm Hg)	
				Found	Reported
1	Benzaldehyde	45	86	42–43	44–45[22]
2	2-Nitrobenzaldehyde	45	87	90–91	90–91[22]
3	3-Nitrobenzaldehyde	45	90	64–65	65–66[22]
4	4-Nitrobenzaldehyde	45	89	124–125	125–127[22]
5	3-Chlorobenzaldehyde	45	90	65–66	64–65[22]
6	4-Chlorobenzaldehyde	45	88	81–82	82–83[22]
7	2,6-Dichlorobenzaldehyde	45	85	88–89	88.5[17]
8	4-Bromobenzaldehyde	45	87	93–94	92–95[20]
9	4-Cyanobenzaldehyde	45	86	100–102	98–102[2]
10	4-Methylbenzaldehyde	45	87	80–81	81–82[22]
11	3-Methoxybenzaldehyde	60	85	Oil	Oil[21]
12	4-Methoxybenzaldehyde	60	82	65–66	64–65[22]
13	4-Acetoxybenzaldehyde	60	85	90–91	89–90[20]
14	4-Acetoxy-3-methoxy benzaldehyde	60	82	90–92	90–91[21]
15	2-Hydroxybenzaldehyde	150	80	100–102	101–103[20]
16	4-Hydroxybenzaldehyde	150	82	90–91	89–90[20]
17	Vanillin	150	80	89–91	90–91[21]
18	Furfural	45	83	51–52	52–53[22]
19	Cinnamaldehyde	45	87	84–86	85–86[22]
20	3-Phenylpropionaldehyde	60	80	Oil	Oil[26]
21	Isobutyraldehyde	45	70	183 (630)	184 (630)[26]
22	Hexanal	60	78	Oil	Oil[26]
23	4-(Dimethylamino)benzaldehyde	180	0	—	—

[a] The yields refer to the isolated pure products.

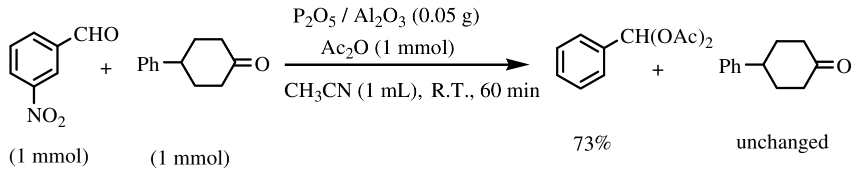
[b] The products were characterized from their spectral (IR, ^1H NMR and MS) and comparison to authentic samples.

Table 3. Competitive acylal formation of aldehydes using Ac_2O in the presence of P_2O_5/Al_2O_3 at room temperature[a]

1



2



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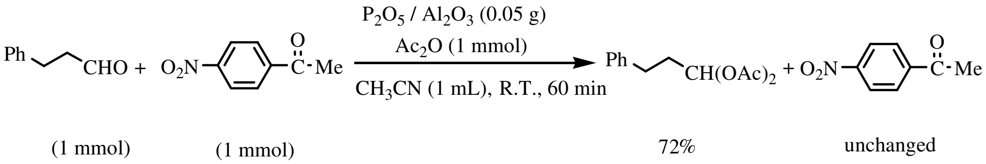

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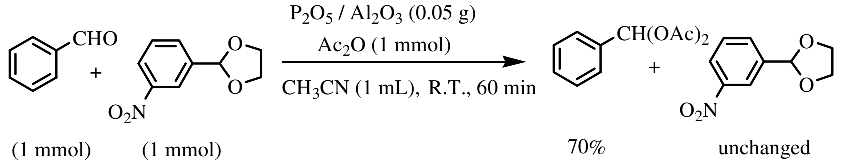

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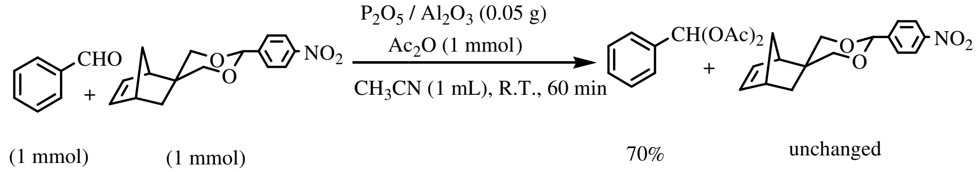

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[a] The yields refer to the isolated pure products.

In conclusion, we report here a mild and efficient catalyst for the preparation of acylals from aldehydes in the presence of acetic anhydride in good yields and short reaction times. This method is highly selective for the synthesis of acylals from aldehydes in the presence of ketones. The use of an inexpensive and relatively nontoxic catalyst and also green reagent is another advantage of this method. In contrast to other acids, storage and handling of this compound do not need special precautions and it can be stored on the bench top for weeks without losing its catalytic activity. Further investigation on the new application of P_2O_5/Al_2O_3 is ongoing in our laboratories.

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33. The reagent was prepared by the combination of phosphorus pentoxide (3 g) and alumina (Al_2O_3, acidic, 3 g) were mixed for 10 min in a sealed round-bottomed flask until a fine and homogenous powder was obtained. This reagent was heated in an oven at 120 °C for 1 h and then stored in a sealed flask for later use. General procedure for the preparation of *gem*-diacetates: To a stirred solution of respective aldehyde (2 mmol) in freshly distilled acetic anhydride (0.48 mL) was added P_2O_5/Al_2O_3 (0.1 g, 15 mol %) and the reaction mixture was stirred at room temperature for the time specified in Table 2. The reaction was followed by TLC (*n*-hexane–EtOAc, 9:1). After completion of the reaction, the mixture was diluted with ethyl acetate and filtered. The organic layer was washed with 10% $NaHCO_3$ solution and saturated solution of $NaHSO_3$ and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give the corresponding pure products.
34. *Typical procedure for the competitive reactions*: To a stirred solution of benzaldehyde (1 mmol), 4-nitroacetophenone (1 mmol) and acetic anhydride (1 mmol) in acetonitrile (1 mL) was added P_2O_5/Al_2O_3 (0.05 g) and the reaction mixture stirred at room temperature for 60 min. The reaction was followed by GC and TLC (*n*-hexane–EtOAc, 9:1). After completion of the reaction, the mixture was diluted with ethyl acetate and filtered. The organic layer was washed with 10% $NaHCO_3$ solution and saturated solution of $NaHSO_3$ and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the product purified by column chromatography on silica gel to give 1,1-diacetoxy-1-phenylmethane in 72%. In this reaction 4-nitroacetophenone was intact.