802 **RESEARCH PAPER** DECEMBER, 802–805 JOURNAL OF CHEMICAL RESEARCH 2004

P_2O_5 / SiO_2 as a mild and efficient reagent for acylation of alcohols, phenols and amines under solvent-free conditions

Hossein Eshghi[a,b*] **and Parvaneh Shafieyoon**[b]

[a]*Department of Chemistry, Ferdowsi University of Mashhad, Mashhad 91775-1436, Iran*

[b]*Department of Chemistry, Sistan and Baluchestan University, Zahedan 98135, Iran*

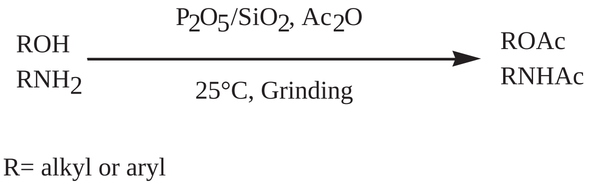
P_2O_5 / SiO_2 is a highly efficient reagent for the acetylations of a variety of alcohols, phenols and amines with acetic anhydride under solvent-free conditions. Primary, secondary, allylic and benzylic alcohols, diols and phenols with electron-donating or withdrawing substituents can be easily acetylated in good to excellent yield.

Keywords: acylation, protection, alcohols, phosphorus pentoxide, silica gel.

Protection of alcohols, amines and phenols is an important and commonly used strategy in organic synthesis.[1] Although a variety of procedures use transesterification methodology,[2] the acylation of alcohols and phenols is routinely[3] carried out using acid anhydrides or acyl chlorides due to the ease of deprotection.[1, 4] DMAP[5] and Bu_3P[6] are known to catalyse this reaction and to increase the rate of acetylations when used as a co-catalyst. The various catalysts developed for the activation of anhydrides include Lewis acids such as $CoCl_2$,[7] $Sc(OTf)_3$,[8] $Sc(NTf_2)_3$,[9] TMSOTf,[10] $Bi(OTf)_3$,[11] $Cu(OTf)_2$,[12] $VO(OTf)_2$,[13] $TaCl_5$,[14] $InCl_3$,[15] zeolites,[16] clays,[17] Nafion-H,[18] yttria-zirconia,[19] $Mg(Br)_2$,[20] LiCl,[21] and $LiClO_4$.[22]

However, most of these procedures suffer from serious drawbacks which include the use of hazardous, highly toxic, flammable, and expensive or commercially unavailable reagents, long reaction times, low yields, drastic reaction conditions and an excess of acylating agents used or of alcohols. In view of the rapidly increasing demands for green chemistry, the practical transesterification and direct esterification should be improved at best to involve mild reaction conditions, decrease the mole ratio of reactants to 1:1, and remove the need for special technology to remove the liberated alcohol (or water).[23]

Recently, we have reported that the P_2O_5 / SiO_2 is an efficient medium for the Fries rearrangement,[24] the Beckmann type rearrangement of ketones[25] and the direct acylation of phenols.[26] In this paper, we describe our findings on the acetylation of the alcohols, phenols and amines with acetic anhydride in the presence of P_2O_5 / SiO_2 in the absence of solvent (Scheme 1).



Scheme 1

Results and discussion

The reaction was affected by simply grinding the substrate, whether it is a solid or liquid, with 1.0–1.5 equivalents of acetic anhydride and the P_2O_5 / SiO_2 reagent with a pestle and mortar at room temperature. Completion of the reaction could be monitored by TLC. The molar quantity of acetic anhydride is quite crucial to the success of the acetylation. When the molar amount of alcohol or phenol and acetic anhydride are equal, the yield of the acetate is moderate and some of the substrate is recovered unchanged. When 1.5 equivalent of acetic anhydride is employed, however, after grinding for 20 min all reactions go to completion. In the cases of diols and amines reactions go to completion with equimolar amounts of acetic anhydride.

The general reaction is illustrated in Scheme 1 and the results are reported in Table 1. All reactions were carried out by simple grinding of the reagents at room temperature under solvent-free conditions for 5–20 minutes. Primary (entries 1–3 and 5), secondary (entries 4, 6, and 9), allylic (entry 8) and benzylic (entry 7) alcohols and phenols (entries 10–17) were easily acetylated in good to excellent yields. In the case of phenols, no competitive Fries rearrangement or direct acylation reactions were observed. We have recently reported[24] that these reactions can be carried out in the presence of the P_2O_5 / SiO_2 reagent at 100°C or under microwave irradiation.

In the cases of the acid-sensitive groups such as with cholesterol, furfuryl and cinamyl alcohols no sign of cyclisation, hydration or decomposition was observed (entries 5, 8 and 9). In order to show the chemoselectivity of the present reagent, the mono-protected diols were treated with acetic anhydride in the presence of the P_2O_5 / SiO_2 reagent at room temperature for 20 min. Only the hydroxyl group was converted into the corresponding acetate and the protective THP group also remained intact (Scheme 2). Notably, the starting mono-protected diols have been prepared selectively from the corresponding diols and DHP in the presence of a catalytic amount of phosphorus pentoxide.[27] However, the observed results showed that the THP groups resist removal in the presence of the modified reagent. We believe that the simple mixing of P_2O_5 and silica gel modified the properties of P_2O_5 and should make the P_2O_5 / SiO_2 reagent less susceptible to moisture circumventing the problem of side reactions for acid-sensitive substrates.

To extend the scope and generality of the use of the P_2O_5 / SiO_2 for this type of process we have also investigated the acetylation of diols, glycerol and D-(+)-glucose. Polyhydroxy compounds were however, transformed into the corresponding polyacetates. No selectivity between primary and secondary hydroxy groups was observed. Attempts at selective acetylation using a lower amount (0.5 equivalent) of Ac_2O in the case of primary diols gave a mixture of mono- and diacetates. All reactions of diols and polyols could be carried out with one equivalent of Ac_2O per hydroxyl group of substrate. The results of acetylation of polyols are reported in Table 2.

Whereas acetylation of diols by metal salt catalysts was unsuccessful,[20] presumably due to irreversible complexation of metal cations by the substrate, thereby reducing its Lewis acidity, selective monoacetylation[28] of symmetric diols adsorbed on silica gel with acetyl chloride was reported by Ogawa *et al.*[29] They suggested that silica gel is considered to play a role as a protecting reagent for the one hydroxyl group of the symmetric diol, which is presumably adsorbed as a monomolecular layer on the surface of silica gel. The observed

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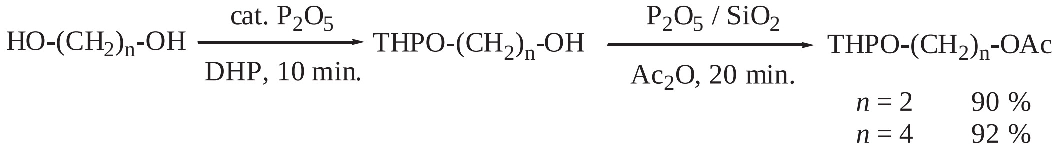
* Correspondence. E-mail: heshghi@hamoon.usb.ac.ir



$$\text{HO-(CH}_2)_n\text{-OH} \xrightarrow[\text{DHP, 10 min.}]{\text{cat. P}_2\text{O}_5} \text{THPO-(CH}_2)_n\text{-OH} \xrightarrow[\text{Ac}_2\text{O, 20 min.}]{\text{P}_2\text{O}_5\text{ / SiO}_2} \text{THPO-(CH}_2)_n\text{-OAc}$$

$n = 2$ 90 %
$n = 4$ 92 %

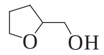
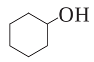
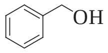
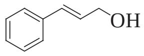
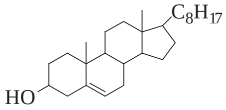
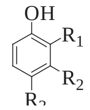
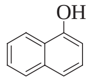
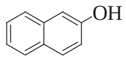
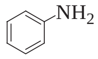
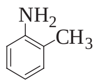
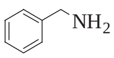
Scheme 2

results with P_2O_5 / SiO_2 showed that the surface of silica gel is preadsorbed with P_2O_5 and cannot act as a protective group for one hydroxyl group. Therefore, even a small amount of Ac_2O yields a mixture of mono- and diacetates. Diacetates can be used as useful precursors for macrocyclic crown ethers synthesis.

In the cases of acetylation of amines (entries 18–21), as mentioned by Chakraborti and Gulhane,[15] we observed that reactions occurred in high yields with one equivalent Ac_2O in the absence of catalyst, although a catalytic amount of P_2O_5 / SiO_2 improved isolated yields.

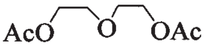
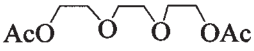
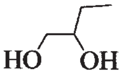
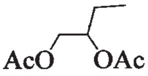
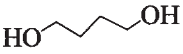
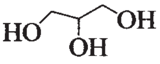
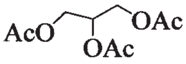
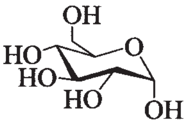
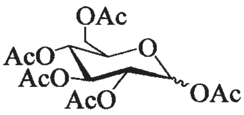
The present procedure with P_2O_5 / SiO_2 provides a very efficient method for the acetylation of alcohols, diols, amines and phenols. The notable advantages of this method are: operational simplicity, ready availability of reagents, and general applicability, mild reaction conditions with a 1–1.5 molar ratio of the reactants, short reaction times and high yields.

Table 1 Acetylation of alcohols, phenols and amines with acetic anhydride in the presence of the P_2O_5 / SiO_2 under solvent-free conditions.

Entry	Substrate	Ratio[a]	Time /min	Yield /%[b]	B.p. °C (Torr) or M.p. °C	
					Found	Reported[ref]
1	$CH_3(CH_2)_6CH_2OH$	1.5:1	20	93	211(760)	212 (760)[17c]
2	$(CH_3)_2CHCH_2CH_2OH$	1.5:1	20	90	142 (760)	141–143 (760)[30]
3	$ClCH_2CH_2OH$	1.5:1	20	80	150 (760)	145 (760)[33]
4	$CH_3CH(OH)(OH)(CH_2)_5CH_3$	1.5:1	20	95	194 (760)	194.4 (744)[32]
5		1.5:1	20	80	205 (760)	193 (760)[33]
6		1.5:1	20	85	173 (760)	175 (760)[32]
7		1.5:1	20	80	216 (760)	230 (760)[17c]
8		1.5:1	20	75	263 (760)	263 (760)[21]
9		1.5:1	20	80	113	113–114[17c]
						
10	$R_1 = R_2 = R_3 = H$	1.5:1	20	95	195 (760)	196 (760)[32]
11	$R_1 = CH_3$; $R_2 = R_3 = H$	1.5:1	20	90	208 (760)	210 (760)[17c]
12	$R_2 = CH_3$; $R_1 = R_3 = H$	1.5:1	20	92	211 (760)	211 (760)[32]
13	$R_3 = CH_3$; $R_1 = R_2 = H$	1.5:1	20	93	213 (760)	212–213 (760)[32]
14	$R_2 = NO_2$; $R_1 = R_3 = H$	1.5:1	20	85	55	53–54[17c]
15	$R_3 = NO_2$; $R_1 = R_2 = H$	1.5:1	20	90	77	76–77.5[17c]
16		1.5:1	20	80	45	45[32]
17		1.5:1	20	80	70	69–70[32]
18		1:1	5	93[c] (90)[d]	115	114[21]
19		1:1	10	96[c] (67)[d]	93	110[32]
20		1:1	5	95[c] (88)[d]	58–59	58–59[25]
21	$CH_3CH_2CH_2CH_2NH_2$	1:1	5	94[c] (85)[d]	228–230 (760)	229(760)[33]

[a] Acetic anhydride: substrate ratio (mol: mol). [b] Isolated yield. [c] Refers to reactions in the presence of the catalytic amount (10 mol %) of the P_2O_5 / SiO_2. [d] Yields in parenthesis refer to reactions in the absence of catalyst.

Table 2 Acetylation of polyols with acetic anhydride in the presence of the P_2O_5 / SiO_2 in solvent-free media

Entry	Substrate[a]	Product	Yield /%[b]	Bp/°C (Torr) or Mp/°C Found	Bp/°C (Torr) or Mp/°C Reported[ref]
1			90	189 (760)	189 (760)[17c]
2			92	206 (760)	200(760)[33]
3			93	289 (760)	286 (760)[33]
4			94	344 (760)[c]	
5			95	196–197 (760)[c]	
6			96	220 (760)	229 (760)[33]
7			90	259(760)	252(760)[17c]
8			85	109	108–110[31]

[a]All reactions of diols and polyols were carried out with one equivalent of Ac_2O per hydroxyl group of the substrate.
[b]Isolated yield.
[c]Tentative structural assignment based on ^1H NMR.

Experimental

All melting points recorded are uncorrected open capillary measurements. IR spectra were recorded on a Shimadzu -IR 470 spectrophotometer. ^1H NMR spectra were recorded on a Bruker-80 MHz instrument using tetramethylsilane (TMS) as an internal standard. Silica gel 60(230–400 mesh) was obtained from Fluka and was dried in an oven at 120°C for 2h. The P_2O_5 / SiO_2 reagent was prepared according to the earlier reported procedure.[25]

Acetylation of alcohols, phenols and amines

General procedure: In a typical reaction, a mixture of alcohol (2 mmol), acetic anhydride (3 mmol) and P_2O_5 / SiO_2 (0.5 g) were ground thoroughly using a pestle and mortar for 20 minutes. The completion of the reaction was monitored by IR and TLC examination. After the completion of the reaction, 10% aqueous hydrochloric acid (15 ml) was added to the mixture which was then extracted with CH_2Cl_2 (2 × 15 ml). The extracts were combined and washed with saturated sodium hydrogen carbonate solution (20 ml) and water (20 ml) and dried over $CaCl_2$. After filtration, evaporation of the solvent under vacuum gave the corresponding acetate esters in high purity (based on TLC, ^1H NMR, IR and melting points). All reactions of diols and polyols (or amines) could be carried out with one equivalent of Ac_2O per hydroxyl (or amino) group of the substrate in the presence of the P_2O_5 / SiO_2.

^1H NMR data of some selected acetates:

Table 1 entry 2: ^1H NMR (80 MHz, $CDCl_3$, 25°C): δ = 0.9 [d, $^3J_{H,H}$ = 8 Hz, 6 H, $(CH_3)_2C$-)], 1.1–1.7 (m, 3 H, $CHCH_2$), 1.9 (s, 3H, CH_3CO–), 3.8 (t, $^3J_{H,H}$ = 8 Hz, 2 H, CH_2O–).

Table 1 entry 3: ^1H NMR (80 MHz, $CDCl_3$, 25°C): δ = 2.2 (s, 3 H, CH_3CO–), 3.8 (t, $^3J_{H,H}$ = 6 Hz, 2 H, CH_2Cl), 4.5 (t, $^3J_{H,H}$ = 6 Hz, 2H, CH_2OAc).

Table 1 entry 5: ^1H NMR (80 MHz, $CDCl_3$, 25°C): δ = 1.2–2.2 (m, 4 H, CH_2CH_2), 2.0 (s, 3 H, CH_3CO–), 3.4–4.2 (m, 5 H, CH_2OCHCH_2OAc).

Table 1 entry 19: ^1H NMR (80 MHz, $CDCl_3$, 25°C): δ = 2.1 (s, 3 H, Ar-CH_3), 2.2 (s, 3 H, CH_3CO–), 6.8–7.4 (m, 4 H, Ar-H), 7.6 (b, 1 H, NH).

Table 2 entry 1: ^1H NMR (80 MHz, $CDCl_3$, 25°C): δ = 2.2 (s, 6 H, CH_3CO–), 4.5 (s, 4H, CH_2OAc).

Table 2 entry 2: ^1H NMR (80 MHz, $CDCl_3$, 25°C): δ = 2.1 (s, 6 H, CH_3CO–), 3.8 (t, $^3J_{H,H}$ = 6 Hz, 4 H, CH_2OCH_2), 4.3 (t, $^3J_{H,H}$ = 6 Hz, 4 H, AcO–CH_2).

Table 2 entry 3: ^1H NMR (80 MHz, $CDCl_3$, 25°C): δ = 1.9 (s, 6 H, CH_3CO–), 3.7 (s, 4 H, CH_2CH_2), 3.75 (t, $^3J_{H,H}$ = 6 Hz, 4 H, CH_2OCH_2), 4.3 (t, $^3J_{H,H}$ = 6 Hz, 4 H, AcO–CH_2).

Table 2 entry 4: ^1H NMR (80 MHz, $CDCl_3$, 25°C): δ = 2.0 (s, 6 H, CH_3CO–), 3.4–3.7 (m, 12 H, $CH_2OCH_2CH_2OCH_2CH_2OCH_2$), 4.2 (t, $^3J_{H,H}$ = 6 Hz, 4 H, AcO–CH_2).

Table 2 entry 5: ^1H NMR (80 MHz, $CDCl_3$, 25°C): δ = 0.9 (t, $^3J_{H,H}$ = 7.5 Hz, 3 H, -CH_3), 1.6 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H, CH_2), 2.3 (s, 6 H, CH_3CO–), 4.1–4.6 (complex, AA, 2 H, AcO–CH_2), 5.2 (m, 1 H, AcO–CH).

Table 2 entry 6: ^1H NMR (80 MHz, $CDCl_3$, 25°C): δ = 1.6 (t, $^3J_{H,H}$ = 4 Hz, 4 H, -CH_2CH_2-), 2.0 (s, 6 H, CH_3CO–), 4.0 (t, $^3J_{H,H}$ = 4 Hz, 4 H, AcO–CH_2).

Received 24 June 2004; accepted 23 October 2004
Paper 04/2596

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