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Silphos [$PCl_{3-n}(SiO_2)_n$]: a heterogeneous phosphine reagent for formylation and acetylation of alcohols and amines with ethyl formate and acetate

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Abstract—Alcohols and amines are formylated and acetylated in the presence of Silphos [$PCl_{3-n}(SiO_2)_n$] in ethyl formate and ethyl acetate in high to excellent yields. This procedure provides a method to separate the product by a simple filtration.

Formylation and acetylation of alcohols is an important transformation in organic synthesis and provides an efficient method for protecting OH groups.[1] Esters are usually synthesized from alcohols and carboxylic acids[2a–l] or acylating/formylating agents such as acyl chloride, acid anhydrides, or an ester.[3a–e] Lewis acid catalysts such as $Sc(OTf)_3$ and $Sc(NTf_2)_3$,[4] $TiCl(OTf)_3$,[5] TMSCl and TMSOTf,[6] $La(Oi\text{-}Pr)_3$,[7] $COCl_2$,[8] $Sn(OTf)_2$,[9] $TiCl_4$/$AgClO_4$,[10] $AlPW_{12}O_{40}$,[11] have been used as catalysts or reagents to mediate the reaction between an alcohol and acylating agent. Alkylation of carboxylates with dialkyl sulfates,[12] alkyl halides,[13] or other reagents[14] are options for this conversion which have higher functional group tolerance, but alkylating agents are available in much less variety than alcohols. The use of dialkylaminopyridines, especially DMAP (dimethylaminopyridine)[15] is another reagent of choice but it is reported to be toxic.[15b]

The use of coupling reagents under Steglich or Mitsunobu conditions[15d,16–18] or nucleophilic phosphine catalysts such as tributylphosphine/excess Et_3N[19] are other methods for esterification of sensitive molecules. However, tertiary phosphines suffer from poor air stability, toxicity, and flammability and separation of the products from the reaction mixture requires an acid wash which can be drawbacks of this approach.

We have recently reported the preparation of Silphos [$PCl_{3-n}(SiO_2)_n$] and its applications for halogenation of alcohols and thiols,[20] deoxygenation of sulfoxides to sulfides and reductive coupling of sulfonyl chlorides to their corresponding disulfides.[21] We now report another application for this heterogeneous phosphine reagent and introduce a simple and practical method for the formylation and acetylation of alcohols and amines (Fig. 1).

The reaction conditions for formylation of alcohols was optimized using the reaction of benzyl alcohol with different amounts of Silphos (0.5–1.5 g). Although 0.6 g of Silphos was enough to formylate 1.0 mmol of benzyl alcohol, the reaction time was long (12 h, Table 1, entry 4). One gram of Silphos was found to be the optimum for 100% conversion of benzyl alcohol to benzyl formate at room temperature in 20 min (Table 1, entry 2).

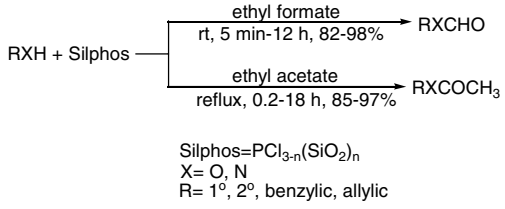

Figure 1. Conversion of alcohols and amines to their corresponding formates and acetates in the presence of Silphos [$PCl_{3-n}(SiO_2)_n$].

Keywords: Silphos; Formylation; Acetylation; Alcohol; Amine; Ethyl formate; Ethyl acetate; Formate; Acetate.
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Table 1. Formylation of 1.0 mmol of benzyl alcohol with different amounts of Silphos in ethyl formate at room temperature

Entry	Silphos (g)	Reaction time	Conversion (%)
1	1.5	2 min	100
2	1.0	20 min	100
3	0.8	3 h	100
4	0.6	12 h	100
5	0.5	24 h	60

Other alcohols and amines were then subjected to the reaction with Silphos in ethyl formate under the optimized reaction conditions and the data are summarized in Table 2.

In order to optimize the reaction conditions for acetylation reactions, 1.0 mmol of 2-phenylethanol was reacted with different amounts of Silphos (0.2–1.5 g) in ethyl acetate at room temperature and also under reflux. It was observed that 0.8, 1.0, and 1.5 g of Silphos gave 100% conversion in 14, 12, and 6 h, respectively. We therefore used 1.5 g of Silphos in refluxing ethyl acetate for acetylation of different alcohols and amines. The results are summarized in Table 3.

To generalize this procedure for the conversion of substrates other than alcohols and amines to their corresponding formates and acetates, thiols, phenols and α-hydroxyphosphonates were reacted under the same reaction conditions as alcohols. Among these substrates, only phosphonates produced α-formyloxy-phosphonates in ~30% yields and the others remained unchanged.

The procedure is very much dependent on steric factors and the nucleophilicity of the hydroxyl or amine group.

Table 2. Formylation of 1.0 mmol of alcohol or amine with 1.0 g of Silphos in ethyl formate at room temperature

Entry	Substrate (%)	Reaction time	Yield (%)
1	Benzyl alcohol	20 min	95
2	4-Methoxybenzyl alcohol	5 min	98
3	4-Bromobenzyl alcohol	2 h	92
4	4-Chlorobenzyl alcohol	2 h	94
5	2-Phenylethanol	15 min	93
6	3-Phenylpropanol	15 min	93
7	Allyl alcohol	5 min	85
8	Isoamyl alcohol	20 min	82
9	2-Octanol	2 h	90
10	Cyclohexanol	1.5 h	91
11	Cinnamyl alcohol	15 min	94
12	Cholesterol	4 h	96
13	(−)-Menthol[a]	1 h	94
14	2-(4-Biphenyl)-2-propanol	24 h	—[b]
15	Aniline	75 min	92
16	*p*-Methoxyaniline	40 min	96
17	Benzylamine	5 min	95
18	4-Chloroaniline	2 h	90
19	Cyclohexylamine	1 h	94
20	*N*-Methyl aniline	12 h	90

[a] Optical rotation of menthyl formate was $[\alpha]_D = -75.5°$, (*c* 1.0, $CHCl_3$), lit.[2k] $[\alpha]_D = -75.3°$ ($CHCl_3$).
[b] The conversion was 50% after 24 h.

Table 3. Reaction of 1.0 mmol of alcohol or amine in the presence of 1.5 g of Silphos in refluxing ethyl acetate

Entry	Substrate	Reaction time (h)	Yield (%)
1	Benzyl alcohol	7	95
2	4-Methoxybenzyl alcohol	2	92[a]
3	4-Bromobenzyl alcohol	12	94
4	4-Chlorobenzyl alcohol	12	91
5	2-Phenylethanol	6	97
6	3-Phenylpropanol	6	95
7	Allyl alcohol	1	88
8	Isoamyl alcohol	3	85
9	2-Octanol	24	—[b]
10	Cyclohexanol	18	89
11	Cinnamyl alcohol	6	90
12	Cholesterol	18	94
13	(−)-Menthol[c]	12	92
14	2-(4-Biphenyl)-2-propanol	24	—[d]
15	Aniline	2	91
16	*p*-Methoxyaniline	1.5	94
17	Benzylamine	0.2	97
18	4-Chloroaniline	4	88
19	Cyclohexylamine	2	94
20	*N*-Methyl aniline	16	92

[a] The conversion was 100% but 5% 4-methoxybenzaldehyde was also produced.
[b] The conversion was 75% after 24 h.
[c] Optical rotation of menthyl acetate was $[\alpha]_D = -79.1°$ (*c* 1.0, $CHCl_3$), lit.[2k] $[\alpha]_D = -79.3°$ (*c* 1.0, $CHCl_3$).
[d] The conversion was about 20% after 24 h.

The reaction mechanism probably involves intermolecular attack of the alcohol or amine to the activated ethyl formate or ethyl acetate so the activity of the alcohol or amine decreases as it gets bulkier.

The mechanism of the reaction is not clear as yet. In the methods reported in the literature for formylation reactions using phosphine reagents, molecular or electrophilic halogens are also involved.[22] In our method, no additional halogen is required and Silphos alone completes the reaction. The catalytic role of HCl is also ruled out since no HCl was produced during the reaction. On this basis, the following probable mechanism for the conversion of alcohols to their corresponding formates and acetates is suggested (Fig. 2).

The method described here is very simple and a filtration removes the oxidized silicaphosphine residue to give the product almost pure in high to excellent yields. The reagent applied for this conversion, Silphos $[PCl_{3-n}(SiO_2)_n]$, is prepared from cheap and easily available starting materials.[20] This procedure represents a highly selective method for the formylation and acetylation of alcohols in the presence of phenols and thiols.

Typical procedure for formylation of benzyl alcohol: To a heterogeneous mixture of 1.0 g of Silphos and 5.0 mL of ethyl formate was added 1.0 mmol of benzyl alcohol (0.1 g) at room temperature. The reaction mixture was stirred and monitored by TLC. After completion of the reaction (20 min), the oxidized Silphos was separated by filtration. The solvent was evaporated. Benzyl formate was produced in 95% yield (0.13 g); bp

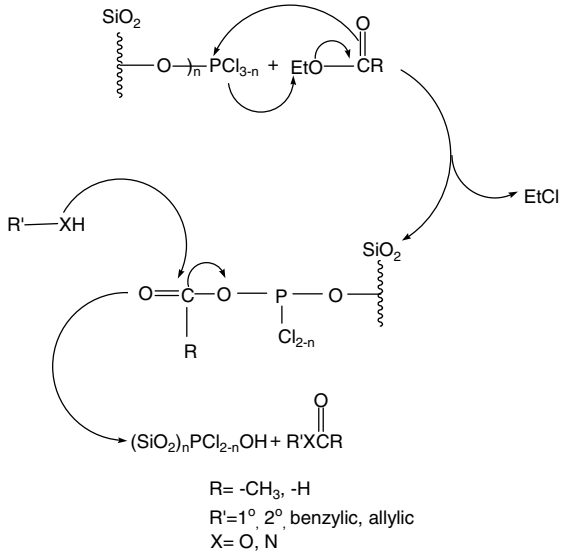

Figure 2. The proposed mechanism for formylation and acetylation of alcohols and amines.

200 °C, lit.[23] bp 201 °C. The product was found to be highly pure by GC analysis.

Typical procedure for acetylation of 2-phenylethanol: 2-Phenylethanol (1.0 mmol, 0.12 g) was added to 1.5 g of Silphos $[PCl_{3-n}(SiO_2)_n]$ in refluxing ethyl acetate (5 mL) and the mixture was stirred. The progress of the reaction was monitored by TLC. After completion of the reaction (6 h), the reaction mixture was filtered in order to separate the oxidized Silphos. The solvent was evaporated giving pure 2-phenylethyl acetate (97%, 0.16 g); bp 229 °C, lit.[24] bp 231–233 °C. The product was found to be highly pure by GC analysis.

Typical procedure for N-formylation of aniline: To a mixture of 1.0 g of Silphos and 5.0 mL of ethyl formate was added 1.0 mmol of aniline (0.09 g) at room temperature. The reaction mixture was stirred and monitored by TLC. After completion of the reaction (75 min), the oxidized Silphos was separated by filtration. The solvent was evaporated giving pure formanilide in 92% yield (0.11 g); mp 45–47 °C, lit.[25] mp 48–50 °C. The product was found to be highly pure by GC analysis.

Typical procedure for N-acetylation of benzylamine: 1.0 mmol of benzylamine (0.1 g) was added to 1.5 g of Silphos $[PCl_{3-n}(SiO_2)_n]$ in refluxing ethyl acetate (5 mL) and stirred. The reaction was monitored by TLC. After 0.2 h, the reaction mixture was filtered in order to separate the oxidized Silphos. The solvent was evaporated giving pure *N*-benzylacetamide (0.145 g, 97%); mp 59–60 °C, lit.[26] mp 61 °C. The product was found to be highly pure by GC analysis.

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