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Alcoholysis and Carbonyl Hydrosilylation Reactions using a Polymer-Supported Trialkylsilane

Yonghan Hu and John A. Porco, Jr.*
Argonaut Technologies, 887 Industrial Road, Suite G
San Carlos, CA 94070 USA

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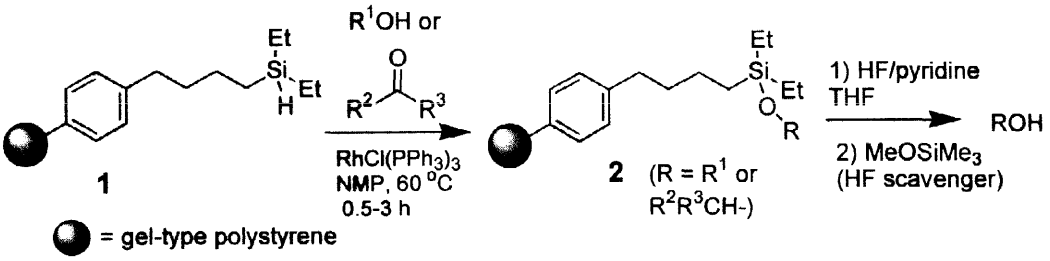
Abstract: Polystyrene-diethylsilane (PS-DES) resin may be reacted with alcohols (alcoholysis) and carbonyl compounds (hydrosilylation) in 1-methyl-2-pyrrolidinone (NMP) using Wilkinson's catalyst ($RhCl(PPh_3)_3$) to afford the corresponding resin-bound silyl ethers. The silyl ethers formed were effectively cleaved using HF/pyridine solution in THF. Methoxytrimethylsilane was employed to scavenge excess HF from product solutions. © 1998 Elsevier Science Ltd. All rights reserved.

Solid-phase organic synthesis has found great success in the combinatorial synthesis of small organic molecules.[1] The choice of suitable supports and appropriate linkers are of utmost importance in synthetic sequences. A variety of linkers have been developed for both carbon- and heteroatom-based attachment.[2] The use of silicon as a linkage element to solid supports has been extensively utilized.[3] Silicon linkers reported thus far require either a reactive (unstable) silyl chloride resin or attachment of silicon linker to scaffolds prior to loading on the support. Hydrosilanes have been utilized for dehydrogenative coupling[4] with alcohols and hydrosilylation of carbonyl compounds in solution.[5] The resulting silyl ethers may be hydrolyzed to afford the corresponding alcohols.[6] Polymer-supported trialkylsilanes with a pendant Si-H functionality thus appeared to be promising for direct attachment of both alcohol and carbonyl compounds. In this article, we present a common procedure for both direct attachment of alcohols and hydrosilylation of carbonyl compounds in 1-methyl-2-pyrrolidinone (NMP) using Wilkinson's catalyst to provide resin-bound silyl ether products (**2**).

Scheme 1



We have recently reported that PS-DES resin (**1**) may be used for the *in-situ* generation of a silyl chloride intermediate and subsequent attachment of oxygen and carbon-based functional groups.[7,8] After considerable experimentation, we found that resin-bound silyl ethers **2** may also be formed by direct

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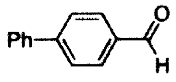
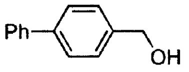
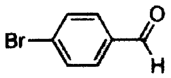
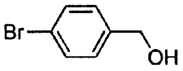
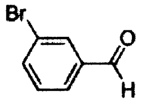
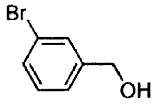
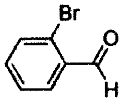
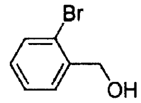
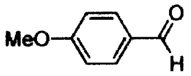
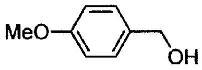
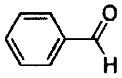
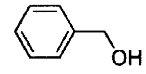
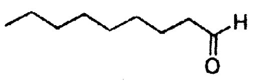
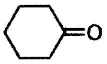
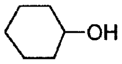
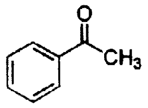
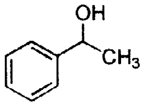
treatment of resin **1** with the appropriate alcohol or carbonyl compound in NMP using $RhCl(PPh_3)_3$ (**Scheme 1**).

Table 1: Hydrosilylation of carbonyls with PS-DES resin using $RhCl(PPh_3)_3$ as catalyst followed by HF cleavage

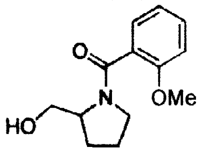
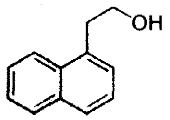
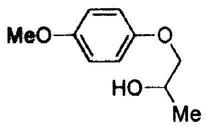
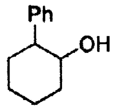
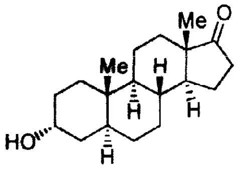
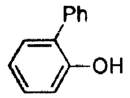
Entry	Carbonyl	Reaction time	Cleavage product	GC yield[a]
1		2h		88%
2		0.5h		65%
3		2h		72%
4		3h		63%
5		2h		77%
6		2h		84%
7		3h		25%[b]
8		3h		61%
9		3h		50%

[a]Yield for two steps (loading/cleavage) based on initial PS-DES silane loading and quantification by GC (anthracene as internal standard). [b] An unidentified byproduct was observed by GC analysis.

The use of NMP as solvent was found to be essential for the success of these transformations; initial studies showed that both silane alcoholysis and hydrosilylation of carbonyls with PS-DES resin in toluene did not proceed to a considerable extent as determined by the presence of residual Si-H IR stretch at 2100 cm^{-1}. Coordinative catalysis of the silicon by NMP may be involved in accelerating the rates of these transformations. A similar effect employing NMP as solvent has recently been reported in the synthesis of arylsilanes *via* Pd-catalyzed silylation of aryl halides with hydrosilanes.[9] In addition, the use of NMP as solvent largely prevented deposition of metallic rhodium on the resin beads. Representative results of the reaction of PS-DES resin with 2 equiv. of carbonyl derivatives (Table 1) and alcohols (Table 2) using 4 mol % $RhCl(PPh_3)_3$ are provided.[10]

Alcoholysis of resin **1** was performed using a variety of alcohols (Table 2), including primary alcohols (entries 1-2), secondary alcohols (entries 3-5), and phenols (entry 6). Direct attachment of Fmoc-aminoalcohol (entry 7) was unsuccessful under the reaction conditions. In the case of epiandrosterone (entry 5), chemoselective dehydrogenative coupling of the hydroxy functionality versus hydrosilylation of the carbonyl group was observed.

Table 2: Alcoholysis of PS-DES resin using $RhCl(PPh_3)_3$ as catalyst followed by HF cleavage

Entry	Alcohol	Reaction time	GC yield[a]
1		2h	87%
2		2h	85%
3		2h	79%
4		3h	66%
5		2h	70%
6		2h	50%
7		5h	no reaction

[a] Yield for two steps (loading/cleavage) based on initial PS-DES silane loading and quantification by GC (anthracene as internal standard).

Cleavage of the resin-bound silyl ethers generated by dehydrogenative coupling or hydrosilylation was performed using a HF/pyridine solution in THF.[10] We have found that excess HF may be scavenged using methoxytrimethylsilane ($MeOSiMe_3$) as evidenced by the neutralization of the HF solution (pH analysis) and the formation of $FSiMe_3$ and MeOH as determined by GC analysis.[10] This method is complimentary to the non-invasive cleavage method of AcOH/THF/H_2O (6:6:1) previously reported[8] and allows direct concentration of cleavage mixtures without further purification.

In summary, a method for the direct loading of alcohols and carbonyl compounds onto a polymer-supported trialkylsilane resin (PS-DES) resin has been developed. In particular, hydrosilylation-based loading allows utilization of carbonyl diversity reagents to afford alcohol-derived products after cleavage. Resin-bound silyl ethers may be cleaved using HF/pyridine solution in THF, and residual HF neutralized using a liquid scavenger, $MeOSiMe_3$ which affords volatile side products. The development and use of other trialkylsilane linkers is in progress and will be reported in due course.

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*Authors to whom correspondence should be addressed: e-mail: fred@argotech.com (Yonghan Hu), jporco@argotech.com (John Porco).

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10. *Representative procedure for the hydrosilylation of carbonyls followed by HF cleavage*: To a 10 mL round-bottom flask was added under argon 500 mg of PS-DES resin (0.375 mmol), 136.7 mg of 4-biphenylcarboxaldehyde (0.75 mmol), 14 mg of $RhCl(PPh_3)_3$ (4 mol %), 5 ml NMP (dried over molecular sieve) and a stirring bar. After heating (60°C) with stirring for 2 h, the mixture was washed with NMP (3 × 5 mL), DCM (3 × 5 mL), and THF (3 × 5 mL). To the washed resin was added a 0.4 M HF/pyridine solution in THF (5 mL). The solution was agitated for 2 h and $MeOSiMe_3$ (Aldrich, 0.5 mL, ~ 2 equiv. to HF used) added and the reaction further agitated for 2 h. The filtrate and the washing solvent (THF) were combined with internal standard (anthracene) for GC quantification. The procedure for the alcoholysis of PS-DES resin is similar to that used for the hydrosilylation of carbonyls.