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One-Pot Reductive Acetylation of Aldehydes using 1-Hydrosilatrane in Acetic Acid

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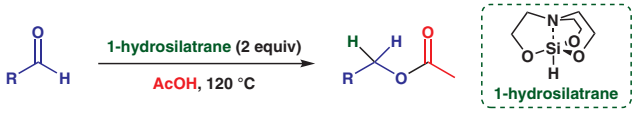

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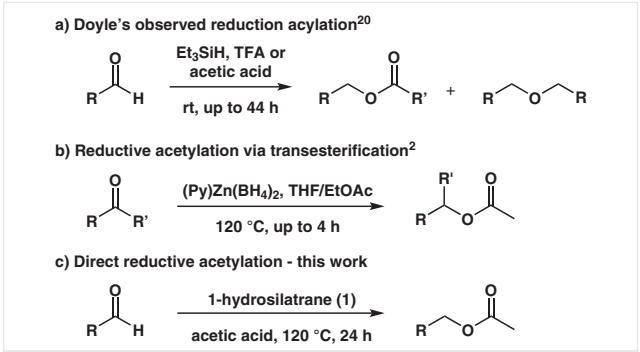
Abstract A one-pot, direct reductive acetylation of aldehydes was achieved under mild conditions using 1-hydrosilatrane as a safe and easily accessible catalyst. Described herein is a facile synthesis that produces acylated primary alcohols that can serve as valuable building blocks for organic synthesis. The method has good functional group tolerance and works for a range of aryl aldehydes, with the notable exception of electron-rich arenes. A library of esters was isolated by flash chromatography in yields as high as 92%.

Key words esterification, reduction, silatrane, one-pot synthesis

The traditional approach for the synthesis of acylated alcohols from aldehydes proceeds via reduction to an alcohol followed by an acylation reaction.[1] Alternatively, reductive acylation is a simple method of obtaining acylated alcohols directly from ketones and aldehydes.[2,3] Such methods find utility in two distinct ways: (1) the synthesis of industrially useful or naturally occurring esters (e.g., polyesters or triglycerides, respectively),[4] or (2) the one-pot synthesis and protection of alcohols as synthetic intermediates (e.g., benzyl ester and acetyl groups).[5] Transforming carbonyl-containing compounds directly into acylated alcohols – as opposed to performing these tasks stepwise – improves the efficiency of multistep synthetic procedures by reducing the required time and energy, as well as the chemical waste produced. Furthermore, the acetate products can be deprotected to their corresponding alcohols under mild conditions.[6,7]

There are existing methods for reductive acylation, many of which involve transition metals.[8–12] Metal-free reactions offer significant advantages (reduced environmental impact and cost, and increased accessibility); however, transition-metal-free approaches to reductive acetylation are rare.[11] The general mechanism for polar reductive acetylation is as follows: the π-bond of the carbonyl of interest (i.e., an aldehyde or ketone) is reduced and further functionalized in situ via either esterification with carboxylic acids or transesterification with another ester.[4] The more explored approach is the second one, using weak reducing agents such as $NaBH_4$ and $ZnBH_4$ in the presence of an ester, most commonly ethyl acetate that doubles as the solvent.[2,3,9,10,13] In the case of the first approach, there is a logistical hurdle to overcome. The most common and efficient way to form an ester directly from a carboxylic acid is via Fischer esterification.[14] However, the Brønsted acid required for this transformation is not compatible with most hydride reducing reagents.[15] Alternatively, one could imagine achieving esterification by using an activated carboxylic acid, such as an acid chloride,[16] but such highly electrophilic species competitively react with any hydride reagent capable of reducing an aldehyde or ketone.

In contrast to common boro-, alumino-, and zinc hydrides, organosilicon hydrides such as triethylsilane not only tolerate acidic conditions but, in some cases, require acidic conditions to act as reducing agents.[17,18] This makes organosilane hydrides potentially useful reagents for applications in reductive acylation of aldehydes and ketones. Triethylsilane in the presence of trifluoroacetic acid has been shown to promote reductive acetylation of aldehydes in moderate to good yield; a significant disadvantage of this unoptimized method being that a substantial proportion of deleterious ether side-product also forms in many cases (Scheme 1a),[19] which is fairly common in acid-catalyzed reductions using hydrosilanes. This finding, however, demonstrates a potential path forward for direct reductive acylation.



Scheme 1 Example methods of reductive acylation

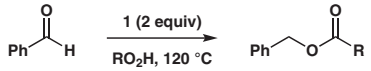
Recently, our group has developed several reductive methods using 1-hydrosilatrane (Figure 1). Our research program has led to the development of a direct route for the reduction of aldehydes and ketones to their corresponding alcohols[20,21] and direct reductive aminations of aldehydes and ketones in the presence of an amine.[22] 1-Hydrosilatrane is an attractive reducing agent because it is air- and moisture-stable, inexpensive, and simple to synthesize.[21] While most of our work has shown silatrane reduction utilizing a Lewis base activator, experimental observations indicate that weak Brønsted acids also facilitate the reduction of aldehydes with no observed ether formation. With this in mind, this work seeks to expand the utility of silatrane by developing a simple and efficient way of synthesizing esters from aldehydes in a single-pot reaction (Scheme 1c) and reports our findings to date towards this aim.

Figure 1 1-Hydrosilatrane

Several variations of the reaction were investigated with benzaldehyde and carboxylic acids using 2 equivalents of 1-hydrosilatrane (Table 1). Trifluoroacetic acid (entry 1) only gave a 10% conversion to product, likely because of acidolysis of 1-hydrosilatrane before complete reduction of the aldehyde. Propanoic acid (entry 2) gave a slightly higher conversion of 25% but was still considerably less effective than acetic acid (entry 3), which gave a conversion of 75%. Increasing the concentration of reactants resulted in an improved conversion of 99%. Isolation of products required flash column chromatography because of the formation of a gel.[23]

The reaction scope was examined by using a variety of aldehydes (Scheme 2).[24] Benzaldehyde provided a 64% yield of **3a**.[25] Benzaldehydes containing electron-withdrawing groups such as nitro, cyano, and acetyl provided yields of 57–92% of **3b–e**. Note that no reduction of the ketone moiety was observed in the reaction to form **3e**, suggesting

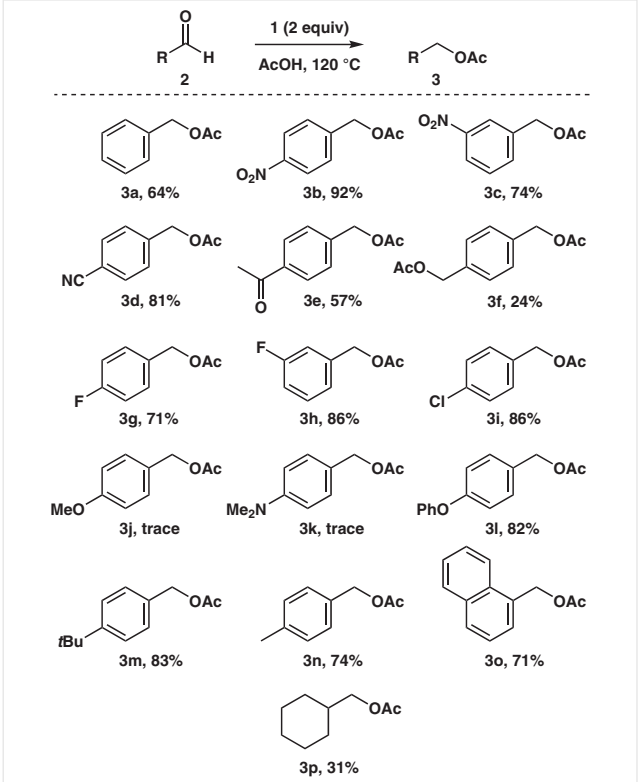
Table 1 Optimization of Carboxylic Acid for the One-Pot Direct Reductive Acylation of Benzaldehyde[a]



Entry	R	Conversion (%)[b]
1	CF_3	10
2	C_2H_5	25
3	CH_3	75
4	CH_3	99[c]

[a] Reaction conditions: Benzaldehyde (5 mmol), 1-hydrosilatrane (10 mmol), carboxylic acid (5 mL), 120 °C, reflux, 24 h.
[b] Conversion (%) determined by GC analysis.
[c] 1 mL of acetic acid used.

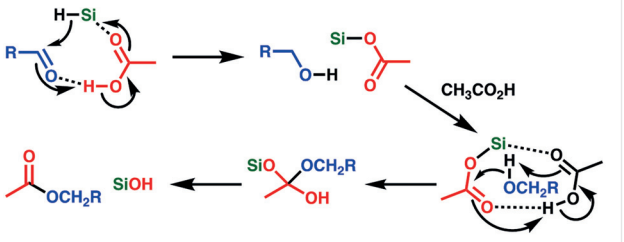
chemoselectivity for the reduction. Terephthaldehyde underwent reduction and esterification on both sites to yield diester **3f** in a poor yield of 24%. Benzaldehydes containing inductively electron-withdrawing fluoro and chloro groups gave 71–86% yields of **3g–i**. Benzaldehydes containing strong electron-donating methoxy and dimethylamino groups only gave trace amounts of **3j–k** (determined as <5% by GC). Benzaldehydes containing weaker electron-donating phenoxy, *t*-butyl, and methyl groups provided the desired products **3l–n** in yields of 74–83%. Reductive esterification of 1-naphthaldehyde resulted in a 71% yield of **3o**.[26]



Scheme 2 Single-pot esterification of aldehydes with acetic acid.

The process was not limited to aromatic aldehydes; the aliphatic cyclohexylcarboxaldehyde readily formed ester **3p**, albeit in a modest isolated yield of 31%.

Overall, a clear relationship between the substituent properties on the aromatic benzaldehydes and the observed yields has been established. Electron-donating groups, which decrease electrophilicity of the carbonyl carbon, slowed the rate of reduction to the corresponding alcohol and hence, overall reaction progression. Electron-withdrawing substituents increase electrophilicity of the carbonyl carbon, ultimately resulting in the highest yields.



Scheme 3 Plausible mechanism for direct reductive acetylation

A plausible mechanism for the observed transformation is shown in Scheme 3. The acetic acid solvent may serve to preorganize and activate the silatrane (as a Lewis base) and the aldehyde (as a Brønsted acid) to enable the hydride reduction. Bidentate coordination of another equivalent of acetic acid to the acylsilatrane could then facilitate transesterification from the silyl ester to the final ester product.

In summary, a facile single-pot esterification method of aldehydes using the readily available 1-hydrosilatrane as a reducing agent has been reported. Although this method is efficient with electron-poor aldehydes, further work needs to be undertaken to broaden its applicability to electron-rich aldehydes, to accommodate a wider range of carboxylic acids.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611697.

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(24) **General Experimental Procedure:** A 25-mL round-bottom flask was charged with a magnetic stirrer bar, 1-hydrosilatrane (10 mmol), and the aldehyde starting reagent (5 mmol) dissolved in acetic acid (5 mL). The flask was capped with a water-cooled reflux condenser and heated to reflux in a silicon oil bath for 24 hours at 120 °C. Following cooling of the mixture to room temperature, the resulting gel/solid was then crushed and suspended or dissolved in 1 M aqueous HCl (ca. 20 mL) before being transferred to a 125 mL separatory funnel. The aqueous mixture was extracted three times with dichloromethane (30–50 mL) and the combined organic extracts were dried over anhydrous sodium sulfate. The solution was then filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using various hexane/ethyl acetate mixtures to afford the purified product
(25) Characterization data for benzyl acetate (**3a**): Yield: 64% (3.2 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.29 (m, 5 H), 5.14 (s, 2 H), 2.13 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9, 136.0, 128.6, 128.2, 66.3, 21.0. IR (ATR): 1738, 1223, 1026, 737, 696 cm^{-1}
(26) Characterization data for naphthalen-1-ylmethyl acetate (**3o**): Yield: 71% (3.55 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.039 (d, *J* = 8.1 Hz, 1 H), 7.93–7.87 (m, 2 H), 7.62–7.45 (m, 4 H), 5.60 (s, 1 H), 2.14 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 133.7, 131.6, 131.5, 129.3, 128.7, 127.5, 126.6, 126.0, 125.3, 123.5, 64.6, 21.0. IR (ATR): 1736, 1221, 1022, 793, 773 cm^{-1}