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Full Paper

Silane Reduction

Silatrane as a Practical and Selective Reagent for the Reduction of Aryl Aldehydes to Benzylic Alcohols

Vladislav Skrypai,[a] Joseph J. M. Hurley,[a] and Marc J. Adler*[a]

Abstract: Hydrosilanes are cheap, readily available substrates, yet they do not see as extensive use for simple carbonyl reductions as borohydrides. Hydrosilane reducing agents broadly fall into one of two general categories: either a) they are easy to handle and require expensive and/or hazardous additives, or b) they are difficult and/or dangerous to handle. This work details the discovery of mild and functional group compatible conditions utilizing hydrosilatrane for the selective reduction of aryl aldehydes to benzylic alcohols without unwanted formation of ethers or deoxygenated products. This method offers significant advances in silane reductions as silatrane is an air- and moisture-stable yet relatively reactive reducing agent that can be used in benchtop open air reactions.

Introduction

The reduction of organic compounds is a vital and ubiquitous reaction. This process is synthetically important on a range of levels, from research laboratories to the processing of wood pulp for paper. The state-of-the-art general reducing agent for organic compounds is sodium borohydride; this method is effective, and has been applied countless times since its development.[1] Because of its prevalence, millions of kilograms of sodium borohydride are produced and used every year.

Hydrosilanes are also versatile reducing agents for a variety of organic functionalities[2] including aldehydes[3] and ketones.[4] Similar to the pervasive borohydrides, the Si–H bond is polarized towards the hydrogen allowing silanes to serve as mild sources of hydride. Silanes are readily and cheaply available, as silicon is the second most abundant element in the earth's crust. Despite this significant advantage with respect both to environmental friendliness and cost as compared to borohydrides, the synthetic community has not yet developed a widely applied, operationally simple, mild, cheap, benchtop method for the reduction of aldehydes using silanes.

The main reason for this state of affairs is that silane reactivity is difficult to tune. While alkylsilanes (such as triethylsilane) are generally easy to handle,[5] they require forceful activation in the form of a Brønsted acid,[6] Lewis acid,[7] Lewis base,[8] or transition metal[9] in the reaction mixture; the method by which these additives catalyze the reaction varies, but their presence is vital to enhance the hydridic nature of the hydrosilane. Silanes bearing more electronegative substituents (such as alkoxy or halide) or multiple hydrides are more reactive, allowing for the development of many excellent methods, yet simultaneously making them difficult – or at least inconvenient – to handle.[10] For example, Nikinov and co-workers have recently described a useful and economical method to reduce carbonyls to alcohols using the readily available polymethylhydrosiloxane (PMHS) with catalytic hydroxide in a sealed vial within a glovebox; this method necessitates the use of carefully sealed reaction vessel and moisture-free techniques as the active reducing agent is the volatile and highly reactive SiH_4.[11]

In 1976, Eaborn and co-workers reported the use of 1-hydrosilatrane (**1**, Figure 1) as a reducing reagent.[12] Silatranes are a well-explored class of molecules that are structurally confined so as to render the silicon effectively pentavalent: the lone pair of the nitrogen – fixed directly opposed to the axial substituent – has been shown to donate into the σ* orbital of the axial substituent.[13] It is presumably by this mechanism that the hydrosilatrane would be activated, with the intramolecular coordination of the nitrogen playing the role of a Lewis base additive. Similar types of intramolecular activation of hydrosilanes have been demonstrated.[14] Because of their structural rigidity, silatranes exhibit remarkable stability when compared to both other pentavalent silanes and other silyl orthoesters.

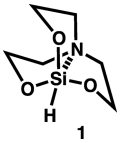

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Figure 1. 1-Hydrosilatrane (**1**).

Since Eaborn et al. disclosed this finding, the enhanced reactivity of hydrosilatrane has been discussed several times in the literature;[2,15] however, we could find no record of it being applied or further explored. Hydrosilatrane is easy to access from inexpensive commercially available substrates and is stable to open air and ambient moisture: for this study, we prepared 1-hydrosilatrane on a multi-gram scale and stored the reagent in a snap-top vial that was frequently uncapped for use without

[a] *Northern Illinois University, Department of Chemistry & Biochemistry, 1425 W Lincoln Hwy, DeKalb, IL 60115, USA,*
mjadler@niu.edu
http://www.themjalab.com

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any special handling, and under these conditions no detectable degradation occurred over the several-month period of the study. For these reasons, silatrane is an attractive option for a mild and user-friendly reducing reagent and we desired to explore the scope for wider application.

Results and Discussion

We were particularly interested in the potential for using hydrosilatrane as a means to mildly and selectively reduce benzaldehydes to benzylic alcohols without the generation of deleterious side products. The singular example of such a reaction from Eaborn et al. (the reduction of *para*-hydroxybenzaldehyde) was reported to afford the corresponding alcohol in low yield (32 %) but seemingly without the appearance of any other products. This is in contrast to what is often found in the silane reduction of aldehydes, as they are frequently accompanied by the formation of symmetric ethers or, particularly in the case of aryl aldehydes, deoxygenated products.[16] While methods have been developed to control the product ratios in known systems, application to novel molecules requires optimization on a case-by-case basis. We were encouraged by the reported result however, as despite the poor yield and forcing conditions (refluxing xylene, 72 h) the reaction was run under highly dilute conditions (0.002 M). Dishearteningly we were unable to reproduce these results using either the original or slightly modified conditions (Figure 2, see Supporting Information for details).

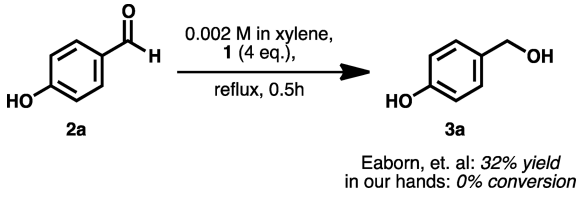


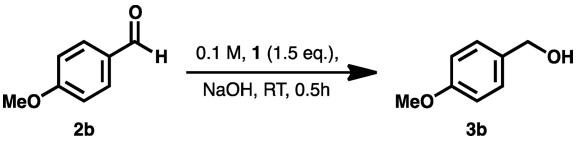
Figure 2. Reduction of 4-hydroxybenzaldehyde (**2a**).

Despite our lack of success in the reduction of aldehydes with silatrane in the absence of additives, we still believed that the silatrane would display enhanced reactivity when compared to alkylsilanes. Recently the reduction of a variety of carbon-heteroatom π bonds through the use of silanes and simple bases has been reported. These reductions predictably were efficient when reactive silanes were utilized, and thus we set out to explore whether silatrane would be a functional reagent in this method.

For optimization, we chose to examine the reduction of *para*-anisaldehyde for several reasons: a) the resulting alcohol has a high enough boiling point to be isolated from high boiling solvents, b) we believed such electron-rich aryl aldehydes would be more challenging to reduce, and c) we did not envision any side reaction with aryl-alkyl ethers. This substrate indeed served as a good model reaction.

Solvent screening (Table 1) showed that both DMF and THF were viable solvents for the conversion of **2b** to **3b**. Solvents were taken directly from a bottle as acquired from the manufacturer and the reaction was set up in an open vessel on the benchtop.

Table 1. Solvent screening for the reduction of *para*-anisaldehyde (**2b**) with hydrosilatrane (**1**).

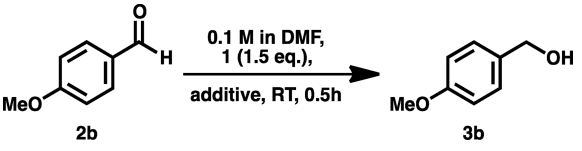


Entry	Solvent	Yield[a] [%]
1	DMF	95
2	THF	87
3	diethyl ether	3
4	acetonitrile	30
5	hexane	3
6	methanol	35
7	dichloromethane	81

[a] Yield determined by NMR spectroscopy.

We next focused on identifying the mildest possible base to enable the activation of silatrane (Table 2). While both sodium and potassium hydroxide efficiently enabled the conversion of *para*-anisaldehyde to the corresponding alcohol, no reaction occurred in the presence of other ionic bases. Additionally, basic amines (primary, secondary, and tertiary) failed to spur any reaction under the attempted conditions.

Table 2. Additive screening for the reduction of *para*-anisaldehyde (2b) with hydrosilatrane (**1**) in DMF.



Entry	Solvent	Additive	Equiv. of additive	Time (h)	Yield (%)
1	DMF	NaOH	30	0.5	95
2	DMF	NaOH	1	24	53
3	DMF	KOH	20	0.5	84
4	DMF	*t*BuOK	1	0.5	80
5	DMF	*i*PrNH$_2$	1.5	1	0
6	DMF	HNEt$_2$	1.5	1	0
7	DMF	NEt$_3$	1.5	1	0
8	DMF	CaCl$_2$	1.5	24	0
9	THF	NaOH	30	0.5	87
10	THF	NaHCO$_3$	10	1	0
11	THF	Na$_2$CO$_3$	10	1	0
12	THF	HCO$_2$Na	1.5	1	0

To demonstrate the unique properties of the silatrane with regard to stability and reactivity, the reaction was attempted with commonly used silane reducing reagents (Figure 3). The first, triethoxysilane, is a highly reactive species that unsurprisingly quickly degraded in the open-air (and hydroxide-containing) solution following partial reduction of the aldehyde. The second, triethylsilane, is a mild and well-behaved reducing agent, which as expected did not undergo any detectable reaction with the aldehyde under the conditions for the observed period of four hours. The reaction proceeded vigorously and relatively well under the conditions using PMHS (85 %), but in the open-air environment silatrane was a more effective reductant.

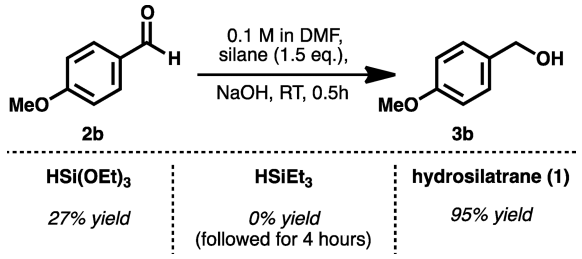
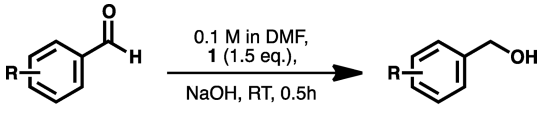


Figure 3. Efficiency of reaction with common silanes.

Finally, the generality of the method was explored: the optimized conditions were applied to a range of commercially available and/or readily synthesized aryl aldehydes (Table 3). Gratifyingly, unsubstituted benzaldehyde **2c** was reduced in excellent yield (Entry 1). Electron-rich aryl aldehydes (e.g. **2d** and **2h**) also were efficiently reduced, even when the substituent was in the *meta* (**2f**) or *ortho* position (**2g**).

Table 3. Reduction of substituted benzaldehydes **2** with hydrosilatrane (**1**).



Entry	R	Aldehyde/alcohol	Yield[a] [%]
1	H	**2c/3c**	98[b]
2	4-*t*Bu	**2d/3d**	95
3	4-Me	**2e/3e**	66[c]
4			92[b,d]
5	4-OMe	**2b/3b**	95
6	3-OMe	**2f/3f**	96
7	2-OMe	**2g/3g**	88
8	4-OPh	**2h/3h**	94
9	4-OBn	**2i/3i**	99
10	4-OAll	**2j/3j**	98
11	4-CN	**2k/3k**	60[c]
12			93[b,d]
13	3-NO_2	**2l/3l**	88[c]
14	4-Cl	**2m/3m**	76[c]
15			98[b,d]
16	4-F	**2n/3n**	98[b,d]
17	3-F	**2o/3o**	28[c]
18			99[b,d]
19	2-F	**2p/3p**	46[c]
20			96[b,d]
21	4-OH	**2a/3a**	0
22			0[e]
23	3-OH	**2q/3q**	44
24			36[e]

[a] Yield determined by NMR unless otherwise noted. [b] Yield determined by GC-FID. [c] Product mixture contained significant amounts (> 5 %) of corresponding benzoic acid. [d] Reaction run under oxygen-free conditions. [e] Reaction run with 2.5 equiv. of **1** for 24 h.

While aldehydes bearing electron-withdrawing groups (including **2k**, **2l**, and **2m**) were well tolerated, the alcohol product was generally accompanied by significant amounts of the corresponding benzoic acid in the crude product mixture. This observation suggested that either a) Cannizaro reaction[17] and/or b) aerobic oxidation were concurrently taking place. The deleterious benzoic acid product was also formed in the attempted reduction of **2e**. Reactions run with **2e**, **2k**, **2m**, and **2o** in the absence of silatrane showed conversion to mixtures of alcohol and carboxylic acid, with the acid being the predominant species; these results indicate that both side reactions may be taking place. In order to minimize the contribution of aerobic oxidation to the generation of unwanted benzoic acid, several substrates were run under oxygen-free conditions; these trials provided clean reductions and no observable benzoic acid (Entries 4, 12, 15, 16, 18, and 20).

Under the investigated conditions, hydrosilatrane (**1**) exhibited no reaction with other reducible functionalities examined, including the nitriles (Entries 11, 12), nitro group (Entry 15), benzyl (Entry 9) and allyl ethers (Entry 10), and halides (Entries 14–20).

Hydroxybenzaldehydes were unfortunately not reduced effectively: while 3-hydroxy- (**2q**, Entry 23) was partially reduced using the described method, 4-hydroxybenzaldehyde (**2a**, Entry 21) remained unmoved. In these cases, bubbling is observed initially, which is consistent with an acid/base reaction occurring between the hydride of the silatrane and the proton of the phenol.[18] Reduction may then occur, though the anionic benzaldehyde substituent significantly decreases the electrophilicity of the aldehyde; this results in decreased reactivity of the *meta* variant (**2q**) and no reaction at all in the *para* derivative (**2a**). Yields in both cases were not affected by increasing both the concentration of silatrane and reaction time (Entries 22, 24).

The method was also applied to heteroatom-containing (**4a**, **4b**, and **4c**) and polycyclic (**4d**, **4e**, and **4f**) aryl aldehydes. In all cases, the reaction proceeded as expected with excellent yields and no observation of side products (Figure 4). This method was also proven to be effective on aliphatic aldehyde **6** (Figure 5).

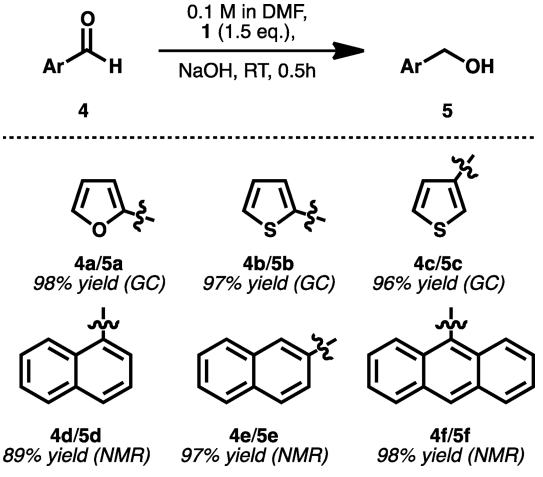


Figure 4. Reduction of non-phenyl aryl aldehydes using hydrosilatrane (**1**).

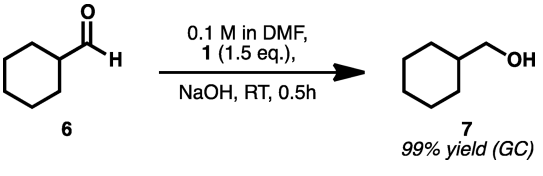


Figure 5. Reduction of an aliphatic aldehyde **6** using hydrosilatrane (**1**).

Conclusions

The reported findings are encouraging for exploration and further development of silatrane reactivity. Cheap and easily accessible hydrosilatrane has been shown to be an effective reductant of aryl aldehydes bearing a variety of functionalities in this user-friendly method. Furthermore, hydrosilatrane demonstrates excellent stability to air and ambient moisture rendering it amenable to benchtop reactions and long-term storage. Further work is currently underway to help elucidate the mechanism of this reaction and also to expand this work to other reducible functionalities.

Experimental Section

General Considerations: All reactions were carried out under ambient conditions in an open vessel, with no special effort to exclude water or air from reaction mixtures unless otherwise noted. Chemicals and reagents were purchased from Sigma–Aldrich and/or Fisher, and were used without further purification unless otherwise noted. ^{1}H NMR spectra were recorded at 500/300 MHz at ambient temperature using a Bruker Avance III spectrometer. The chemical shifts in ^{1}H NMR spectra are reported relative to residual $CHCl_3$ in $CDCl_3$ (δ =7.27 ppm). The chemical shifts in ^{13}C NMR spectra are reported relative to residual $CHCl_3$ in $CDCl_3$ (δ =77.23 ppm). The yields were determined using mesitylene as an internal standard in $CDCl_3$. The abbreviations used for the chemical shifts are as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), dt (doublet of triplets), td (triplet of doublets), dq (doublet of quartets), m (unresolved multiplet).

Synthesis of Silatrane via Boratrane: To a 25 mL flask was added boric acid (50 mmol) and triethanolamine (50 mmol). Water (3 mL) was added to facilitate solubility. The flask was equipped with a short path distillation apparatus and heated to 120 °C until no more water condensed. The isolated boratrane was recrystallized from acetonitrile and used directly in the next step. The experimental data collected are in agreement with those described in the literature.[1] 70 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.65 (t, J = 5.5 Hz, 6 H), 3.04 (t, J = 5.5 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) 62.1, 59.3. IR (ATR) 2988, 2853, 1469, 1370, 1258, 1160, 1115, 1063, 1026, 1001, 933, 889, 730, 621, 560.

To an oven-dried, argon-flushed 100 mL flask containing boratrane (5 mmol) in mixed xylenes (40 mL), was added triethoxysilane (6 mmol) and anhydrous $AlCl_3$ (0.05 mmol). The reaction was refluxed over 4 h and then cooled to room temperature. The resulting solids were filtered and further recrystallized from xylene to give silatrane as white fibrous crystals. The experimental data collected are in agreement with those described in the literature.[19] 88 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.94 (s, 1 H), 3.83 (t, J = 6 Hz, 6 H), 2.89 (t, J = 6 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) 57.2, 51.2. IR (ATR) 2975, 2936, 2886, 2087, 1487, 1457, 1347, 1268, 1090, 1047, 1020, 926, 860, 748, 630, 591.

General Method for the Reduction of Aryl Aldehydes: To a 2 dram vial containing a stir bar was added silatrane (0.15 mmol), aryl aldehyde (0.1 mmol), and DMF (1 mL). The solution was stirred for 5 min to allow for all the silatrane to dissolve, after which additive (1 pellet of NaOH finely ground) was added. After 30 min of stirring in ambient conditions the solution was washed once with 1 M HCl, then extracted three times with dichloromethane and once with diethyl ether. The resulting organic extract was concentrated under reduced pressure and used to determine yield without any further purification. All of the alcohols synthesized are known compounds.

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Keywords: Reduction · Silanes · Silatrane · Lewis bases · Aldehydes

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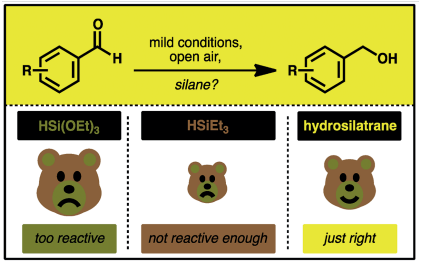
*V. Skrypai, J. J. M. Hurley, M. J. Adler** 1–6

Silatrane as a Practical and Selective Reagent for the Reduction of Aryl Aldehydes to Benzylic Alcohols



Hydrosilatrane was shown to convert aryl aldehydes to alcohols in high yields using hydroxide as a Lewis base activator. This practical silane reducing reagent is more reactive than trialkylsilanes, yet air- and moisiture-stable unlike standard reactive trialkoxysilanes.

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