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Key Organosilane Reductions

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Key organosilane reductions

Dr Gerald Larson of **Gelest** summarises some of the reduction possibilities with silanes

The Si-H bond, based on the relative electrongativities of Si (1.90) and H (2.20), is polarised such that the hydrogen is slightly hydridic in nature. The fact that the silanes are not strongly hydridic makes them excellent candidates for mild and selective reductions of organic functional groups.

Under ionic conditions, it is essentially a requirement that the substrate to be reduced should provide a carbocationic intermediate in order to be reduced effectively by the silane. Thus the reactions are commonly carried out in the presence of an acid catalyst, with trifluoroacetic acid being particularly useful in a number of instances.

The variety of available organosilane structures and the relative ease of the syntheses of this class of organosilane make it possible to alter the organosilane electronically and/or sterically to provide derivatives that allow for the control of reactivity, stereoselectivity and work-up conditions, while also having the potential for recycling the silicon-containing by-product.

Organosilanes have low toxicity, are stable in air and are easily handled, although they will react with acid or base to generate hydrogen gas. Ionic and transition-metal-catalysed organosilane reductions have recently been comprehensively reviewed.[1]

There are many organosilanes to choose from for the various organic reductions. Among the most popular is triethylsilane, which has a convenient boiling point and is easily handled. The least expensive on a per-equivalent of Si-H basis is polymethylhydrogensiloxane (PMHS). Figure 1 lists the more popular organosilanes, their by-products after reaction and an estimate of price on a per-hydride basis.

The direct reduction of **alcohols** to alkanes, which usually involves conversion of the alcohol to a good leaving group followed by reduction with a strong metal hydride reagent, can be carried out directly in a single step with organosilanes. The ease of reduction and the catalyst required depend upon the nature of the alcohol. For example, benzylic, secondary, or tertiary alcohols are reduced to the hydrocarbon in the presence of trifluoroacetic acid or boron trifluoride.[2,3]

The potential rearrangement of the intermediate carbocations must always be considered in these reactions. Primary alcohols are reduced by triethylsilane with tris(pentafluorophenyl)boron as the catalyst (Figure 2a). The reaction stops with the non-reductive triethylsilylation of the alcohol if only a single equivalent of the silane is used.[4,5]

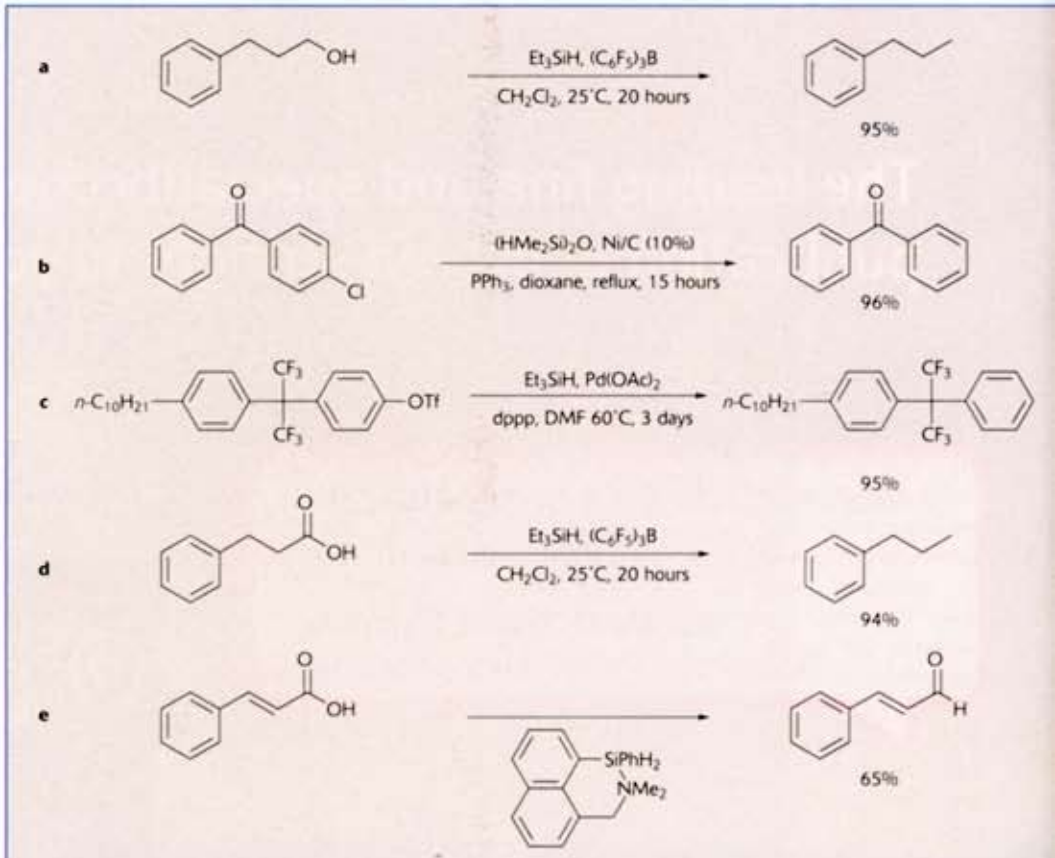

Figure 2 - Reductions of alcohols, halides & carboxylic acids

Silane	Boiling point (°C)	Silane by-product	Cost/mole hydride ($) 1,000 kg scale
Et_3SiH	108	Et_3SiOH +/or Et_3Si–O–$SiEt_3$	9.90
n-$BuMe_2SiH$	101	n-$BuMe_2Si$–O–$SiMe_2Bu$-n	6.97
$PhMe_2SiH$	156	$PhMe_2SiOH$ +/or $PhMeSi$–O–$SiMe_2Ph$	9.60
$PhSiH_3$	120	Phenyl resin	64.00
Ph_2SiH_2	96/13	$Ph_2Si(OH)_2$	53.35
PMHS	–	Silicone resin	0.90

Figure 1 - Common organosilanes

The reduction of **alkyl halides** is possible in a number of ways that compete well with organosilane methods. On the other hand, organosilanes have been shown to reduce aryl halides and triflates in good yields (Figure 2b-c).[6,7]

The reduction of **carboxylic acids** normally requires conversion to the ester, which typically is limited to the isolation of the alcohol. Direct reduction can be accomplished with borane. The use of triethylsilane and trifluoroacetic acid has been shown to reduce carboxylic acids to the trifluoroacetate ester of the alcohol, i.e. reduction to the alcohol, followed by esterification with trifluoroacetic acid.[8]

Direct reduction to the corresponding alcohol can be achieved in good yields with $EtMe_2SiH$ and a ruthenium catalyst.[9] The tris(pentafluorophenyl)-boron-catalysed reduction of carboxylic acids leads to the corresponding alkane in high yields (Figure 2d).[10,11] Isolation of the intermediate triethylsilyl ether of the alcohol is also possible.[11]

In a highly useful transformation, the internally activated silane, 1-(phenylsilyl)-7-dimethylaminomethylnaphthalene, reduces carboxylic acids to the aldehyde (Figure 2e).[12] A similar silane, 1-

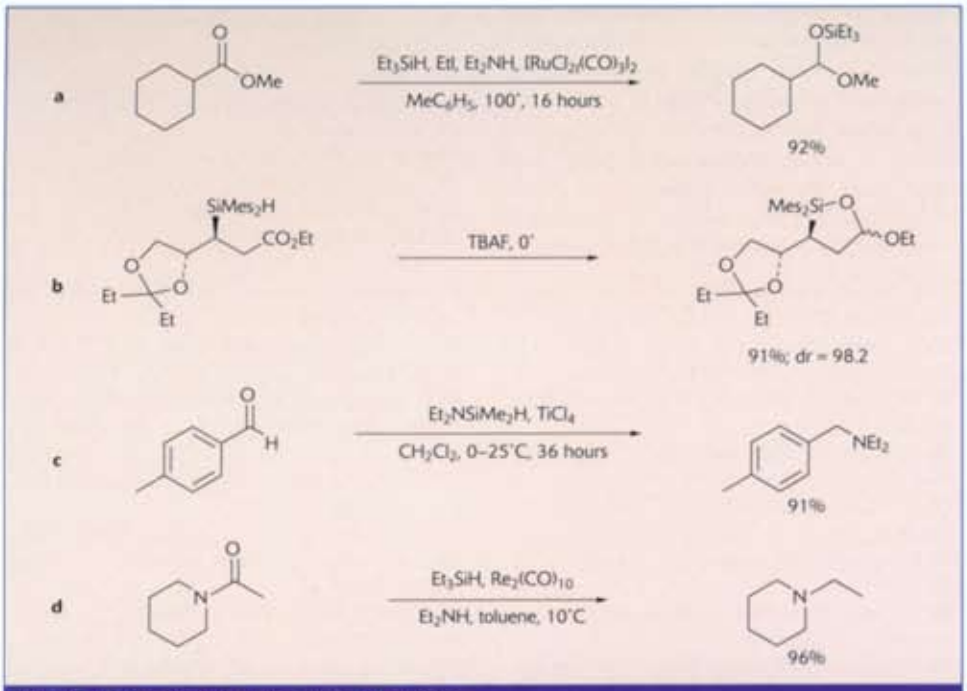

Figure 3 - Reductions of esters, amines & amides

(phenylmethylsilyl)-7-dimethylaminonaphthalene, reduces acid chlorides to aldehydes in excellent yields.[13]

The reduction of **esters** to alcohols is a well-known conversion that can be carried out by a number of processes. The reduction of an ester to an aldehyde, however, is a more difficult process requiring highly selective reducing agents. The combination of $Et_3SiH/EtI/Et_2NH/[RuCl_2(CO)_3]_2$ reduces esters to the corresponding silylated hemiacetal in good yields (Figure 3a).[14]

Other methods, including $Et_3SiH/(C_6F_5)_3B$ or $Ph_3SiH/(C_6F_5)_3B$ also work well for this transformation.[10,11,15] Simple hydrolysis of the silylated hemiacetal provides the aldehyde. An intramolecular example is shown with fluoride catalysis (Figure 3b).[16,17] With *tert*-butyl esters the reduction with Et_3SiH/TFA occurs at the *tert*-butyl group to saponify the ester and give isobutane and the free acid.[18]

The **reductive amination** of aldehydes with the intriguing reagent (diethylamino)dimethylsilane, wherein the silane reagent provides both the hydride and the amine, can be accomplished in good yield (Figure 3c).[19] Alternatively, the silane can provide the reduction in the presence of the amine.[20]

In addition, high-yield reductive aminations of aldehydes with PHMS and the amine have been reported.[21] These kinds of reactions provide useful alternatives to the cyanoborohydride and related borohydride approaches.

The reduction of **amides** to amines is typically carried out with borane or borane derivatives. This

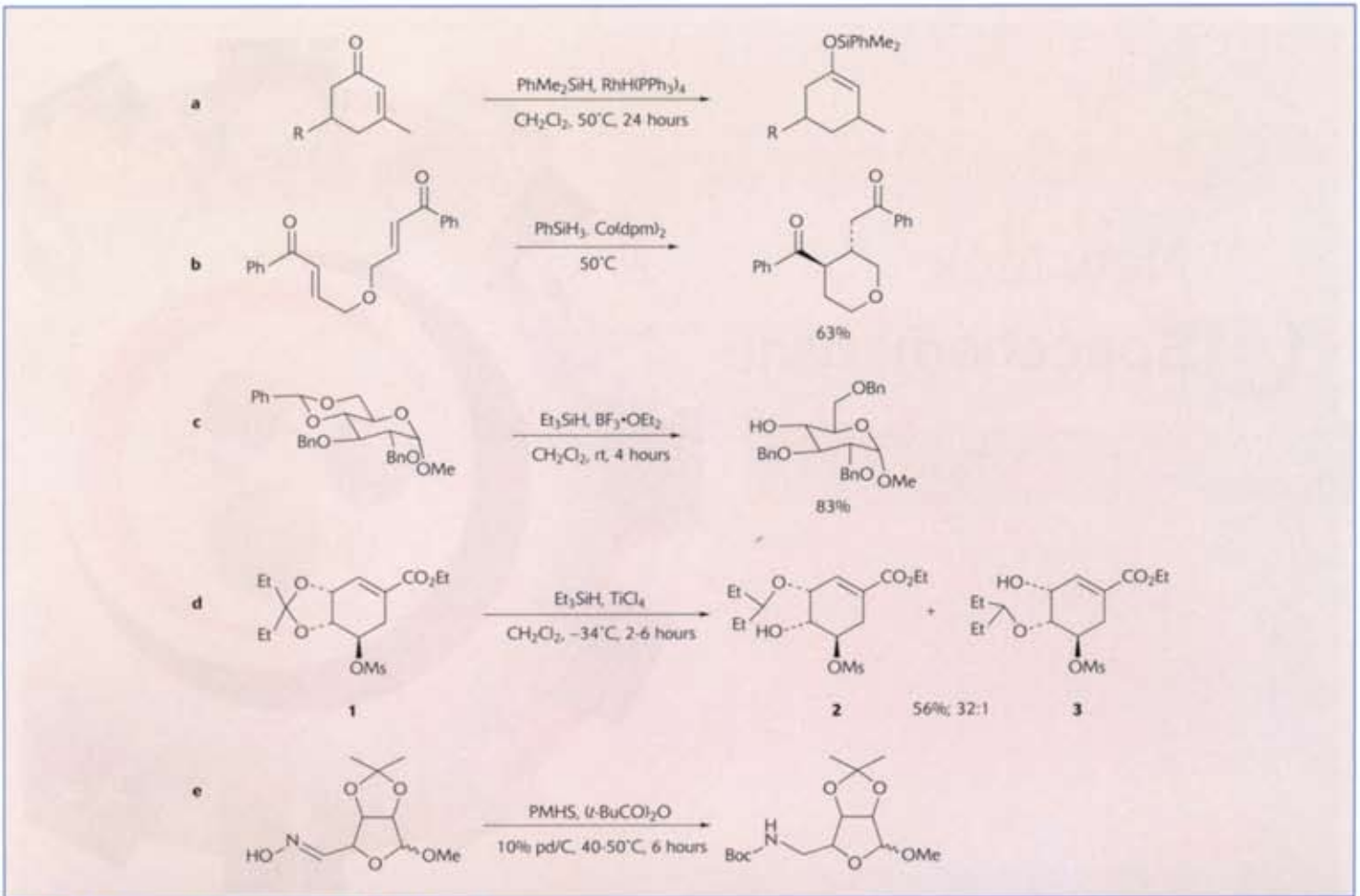

Figure 4 - Reductions of enones, acetals, ketals & oximes

transformation can be accomplished with the more easily handled organosilanes with ruthenium catalysis as well as other transition metal catalysts resulting in high yields under modest reaction conditions (Figure 3d).[22] In a very useful transformation the combination of diphenylsilane and titanium tetraisopropoxide gives good yields of the aldehyde from the amide.[23]

The reduction of **enones** can be accomplished in a 1,2- or a 1,4-manner (Figure 4a).[24] The 1,4-reduction introduces the hydride at the β-carbon with the silicon reacting with the oxygen resulting in the intermediacy of an isolable enol silyl ether, thus providing a convenient route to regioselectively-generated enol silyl ethers (Figure 4b).[25] The 1,4-reduction has been employed in a tandem 1,4-hydrosilylation/Michael addition of bis(enones).[26,27]

The ability of **acetals and ketals** to form a relatively stable carbocationic intermediate upon reaction with an acid makes them excellent candidates for silane reductions. This can be exploited in sugar chemistry.[28]

This ability was employed in the reduction of a benzaldehyde acetal in the presence of an anomeric acetal of a sugar (figure 4c).[29] The high regioselectivity of the triethylsilane reduction of **1**, to produce isomer **2** over isomer **3** is an important step in the synthesis of the 'bird flu' drug, Tamiflu (Figure 4d).[30]

The organosilane reduction of oximes in the presence of $(Boc)_2O$/Pd-C results in the reduction of the **oxime** and Boc-protection of the resulting amine.[31] A similar protocol in the reduction of azides gives the Boc-protected amine (Figure 4e).[32,33] Finally, a large number of organosilane enantioselective reductions have been reported.[1]

References:

1. G.L. Larson, J.L. Fry & S.E. Denmark (eds.) *Organic Reactions*, **2008**, *71*, 1-737
2. H. Duddeck & D. Rosenbaum, *J. Org. Chem.* **1991**, *56*, 1707
3. J.L. Fry, USP 4,130,574, **1978**
4. V. Gevorgyan, J.-X. Liu, M. Rubin, S. Benson & Y. Yamamoto, *Tetrahedron Lett.* **1999**, *40*, 8919
5. V. Gevorgyan, M. Rubin, S. Benson, J.-X. Liu & Y. Yamamoto, *J. Org. Chem.* **2000**, *65*, 6179
6. B.H. Lipshutz, T. Tomioka & K. Sato, *Synlett* **2001**, 970
7. H. Kotsuki, P.K. Datta, H. Hayakawa & H. Suenaga, *Synthesis* **1995**, 1348
8. M.I. Kalinkin, G.D. Kolomnikova, Z.N. Parnes & D.N. Kursanov, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1976**, *25*, 1794
9. S.W. Breeden & N.J. Lawrence, *Synlett* **1994**, 833
10. G.B. Bajracharya, T. Nogami, T. Jin, K. Matsuda, V. Gevorgyan & Y. Yamamoto, *Synthesis* **2004**, 308
11. V. Gevorgyan, M. Rubin, J.-X. Liu & Y. Yamamoto, *J. Org. Chem.* **2001**, *66*, 1672
12. R.J.P. Corriu, G.F. Lanneau & M. Perrot, *Tetrahedron Lett.* **1987**, *28*, 3941
13. B. Becker, R.J.P. Corriu, C. Guérin, B. Henner & Q. Wang, *J. Organomet. Chem.* **1989**, *359*, C33
14. M. Igarashi, R. Mizuno & T. Fuchikami, *Tetrahedron Lett.* **2001**, *42*, 2149
15. D.J. Parks & W.E. Piers, *J. Am. Chem. Soc.* **1996**, *118*, 9440
16. A.P. Davis & S.C. Hegarty, *J. Am. Chem. Soc. 1992, 114*, 2745
17. M.S. Newman & K. Kanakarajan, *J. Org. Chem.* **1980**, *45*, 2301
18. A. Mehta, R. Jaouhari, T.J. Benson & K.T. Douglas, *Tetrahedron Lett.* **1992**, *3*, 5441
19. K. Miura, K. Ootsuka, S. Suda, H. Nishikori & A. Hosomi, *Synlett* **2001**, 1617
20. B.-C. Chen, J.E. Sundeen, P. Guo, M.S. Bednarz & R. Zhao, *Tetrahedron Lett.* **2001**, *42*, 1245
21. S. Chandrasekhar, Ch.R. Reddy & M. Ahmed, *Synlett* **2000**, 1655
22. M. Igarashi & T. Fuchikami, *Tetrahedron Lett.* **2001**, *42*, 1945
23. S. Bower, K.A. Kreutzer & S.L. Buchwald, *Angew. Chem., Int. Ed.*. **1996**, *35*, 1515
24. I. Ojima & T. Kogure, *Organometallics* **1982**, *1*, 1390
25. G.Z. Zheng & T.H. Chan, *Organometallics* **1995**, *14*, 70
26. L.-C. Wang, H.-Y Jang, Y. Roh, V. Lynch, A.J. Schultz, X. Wang & M.J. Krische, *J. Am. Chem. Soc.* **2002**, *124*, 9448
27. T.-G.Baik, A.L. Luis, L.-C. Wang & M.J. Krische, *J. Am. Chem. Soc.* **2001**, *123*, 5112
28. J. A. Bennek & G.R. Gray, *J. Org. Chem.* **1987**, *52*, 892
29. S.D. Debenham & E.J. Toone, *Tetrahedron: Asymmetry* **2000**, *11*, 385
30. M. Federspiel, F. Fischer, M. Hennig, H.-J. Mair, T. Oberhauser, G. Rimmler, T. Albiez, J. Bruhin, H. Estermann, C. Gandert, V. Göckel, S. Götzö, U. Hoffmann, G. Huber, G. Janatsch, S. Lauper, O. Röckel-Stäbler, R. Trussardi & A.G. Zwahlen, *Org. Proc. Res. Dev.* **1999**, *3*, 266
31. S. Chandrasekhar, M.V. Reddy & L. Chandraiah, *Synlett* **2000**, 1351.
32. S. Chandrasekhar, L. Chandraiah, Ch.R. Reddy & M.V. Reddy, *Chem. Lett.* **2000**, 780
33. M. MacDonald, D. Vander Velde & J. Aubé, *J. Org. Chem.* **2001**, *66*, 2636

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