Pentaco-ordinate Silicon Compounds in Synthesis: Chemo- and Stereo-selective Reduction of Carbonyl Compounds using Trialkoxy-substituted Silanes and Alkali Metal Alkoxides

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Carbonyl compounds are reduced with trialkoxy-substituted silane to the corresponding alcohols chemo- and stereo-selectively in the presence of alkali metal alkoxide under mild conditions; reduction occurs very smoothly by using an alkoxide derived from pinacol as a bidentate ligand.

The reduction of carbonyl compounds is one of the fundamental and most important synthetic reactions and efficient methods are highly desirable. The established method is based on the reduction using metal hydrides,[1] and recently tri-substituted silanes,[2] readily available and easily handled, were shown to be reducing reagents with the aid of acid,[3] fluoride ion,[4] and transition metal complexes.[5] We now report that an active species derived from a trialkoxy-substituted silane (**3**) and an alkali metal alkoxide (**4**), especially sodium and lithium pinacolates, reduces aldehydes and ketones (**1**) very smoothly at room temperature to give the corresponding alcohols (**2**) in quite high yields. The reduction takes place in chemo- and stereo-selective mode as shown in equation (1) and the results are listed in Table 1.

$$\underset{(\mathbf{1})}{R^1R^2C{=}O} \xrightarrow[\text{Et}_2\text{O, room temp.}]{\underset{(\mathbf{3})\qquad(\mathbf{4})}{\text{HSi(OR)}_3\text{–MOR}'}} \underset{(\mathbf{2})}{R^1R^2CHOH} \tag{1}$$

The reaction of trimethoxysilane (1.2 mmol) with benzaldehyde (1 mmol) in the presence of lithium methoxide (1.2 mmol) proceeds very smoothly in anhydrous diethyl ether for 20 h at room temperature to afford benzyl alcohol in 85% yield after acid hydrolysis. Approximately 40 and 90% consumption of the aldehyde is observed after 0.5 and 3 3 hours, respectively, and the reaction is almost complete within 6 hours. The reduction proceeds even at 0 °C though more than one day is required for the completion of the reaction but at reflux temperature the yield of the alcohol drops considerably (65%), presumably due to the instability of the active species in the reduction. It should be emphasized that the aldehyde was selectively converted into the alcohol, but the ketone was not reduced when an equimolar mixture of benzaldehyde (1 mmol) and acetophenone (1 mmol) was treated with trimethoxysilane–lithium methoxide (1.2 mmol) in diethyl ether. Triethoxysilane and diethoxymethylsilane can also be used as the reducing reagent (**3**), the reduction being rather slow, however. Sodium methoxide (91% yield), potassium methoxide (88%), and alkali metal alkoxides of ethanol (*e.g.* trimethoxysilane–lithium ethoxide: 85%) are also effective for this conversion. In particular, the reaction with potassium methoxide proceeds rapidly within 2 hours, although the reaction using lithium alkoxide is most convenient. However, aliphatic, alicyclic, and aromatic ketones such as octan-2-one, cyclohexanone, acetophenone, and propiophenone could not be reduced by this reducing system. In contrast, it was found that pinacolates of lithium and sodium were most expedient and effective in promoting the reduction of both aldehydes and ketones, among various bidentate alkali metal alkoxides examined. Since pyrocatecholates of lithium and sodium seem to be unstable at room temperature, satisfactory results were not necessarily obtainable under the present conditions. In addition, ethylene glycolates and trimethylene glycolates of alkali metals did not sufficiently promote the reaction under the present conditions.

Table 1. Reduction of carbonyl compounds (**1**) with $HSi(OMe)_3$ (**3**) to give alcohols (**2**).

Entry	Carbonyl compound (**1**)	Reducing system[a]	Reaction time/h	% Yield[b] of (**2**)
1	Benzaldehyde	A	20	85
2	*o*-Nitrobenzaldehyde	A	15	55
3	*p*-Methoxybenzaldehyde	A	15	86
4	Octan-1-al	A	6	80
5	Acetophenone	B	20	97
6	*p*-Bromoacetophenone	B	15	94
7	Propiophenone	B	15	93
8	Benzophenone	B	15	79
9	2-Tetralone	B	15	86
10	2-Furyl methyl ketone	B	15	68
11	Octan-2-one	B	15	81
12	Cyclohexanone	B	15	83
13	Cycloheptanone	B	15	76

[a] System A: $HSi(OMe)_3$ (1.2 mmol), LiOMe (1.2 mmol), aldehyde (1 mmol); B: $HSi(OMe)_3$ (1.2 mmol), $LiOCMe_2CMe_2OLi$ (2.4 mmol), ketone (1 mmol). [b] Isolated yields; not optimized.

Esters and nitriles were not reduced even by trimethoxysilane–dilithium pinacolate. In addition to the chemoselectivity, the reduction of 2-methylcyclohexanone reveals high stereoselectivity, *cis*-2-methylcyclohexanol being obtained with 85% selectivity.

In a typical procedure dilithium or disodium pinacolate [2.4 mmol; 4.8 ml of a stock solution (0.5 M in hexane–diethyl ether) which was prepared from pinacol and n-butyl-lithium or sodium hydride] was added to the ketone (**1**) (1.0 mmol) in diethyl ether (15 ml) and treated with methoxysilane (134 mg, 1.2 mmol) at room temperature. The suspension was stirred at the same temperature for the time indicated in Table 1. Diethyl ether (20 ml) and hydrochloric acid (1 M, 10 ml) were then added and the mixture was stirred for 1 h. Usual work-up and preparative thin layer chromatography on silica gel gave the pure alcohol (**2**).

$$[M]^+[Z\text{–}Si(OCR_2CR_2O)_2]^-$$

(**5**)

About two decades ago Frye reported that the stable pentaco-ordinate silicon compounds (**5**) could be prepared from alkoxysilanes and 1,2-dialkoxides such as pyrocatecholates of many bases.[6] However, to our knowledge, these alkoxy-substituted pentaco-ordinate silicon compounds have not been applied in organic synthesis, in sharp contrast with the successful use of fluorosilicates.[7] The results summarized in this report strongly suggest that the reduction takes place by *in situ* generated pentaco-ordinate silicon hydrides like (**5**, Z = H).[6]† The present reaction demonstrates an extremely convenient, useful, mild, and chemo- and stereo-selective means of transforming carbonyl compounds into alcohols. Additional aspects of this class of reactions including isolation of (**5**, Z = H), asymmetric induction, and stereocontrolled reduction in the acyclic system are currently under active investigation.

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References

1 H. O. House, 'Modern Synthetic Reactions,' Benjamin, Menlo Park, California, 2nd edn., 1972, pp. 45—105.

2 For reviews, E. Colvin, 'Silicon in Organic Synthesis,' Butterworths, London, 1981, ch. 21, pp. 325—336; W. P. Weber, 'Silicon Reagents for Organic Synthesis,' Springer-Verlag, Berlin, 1983, ch. 17 and 18, pp. 273—297.

3 D. N. Kursanov, Z. N. Parnes, and N. M. Loim, *Synthesis*, 1974, 633.

4 J. Boyer, R. J. P. Corriu, R. Perz, and C. Reye, *Tetrahedron*, 1981, **37**, 2165; R. J. P. Corriu, R. Perz, and C. Reye, *ibid.*, 1983, **39**, 999; C. Chuit, R. J. P. Corriu, R. Perz, and C. Reye, *Synthesis*, 1982, 981; M. Fujita and T. Hiyama, *J. Am. Chem. Soc.*, 1984, **106**, 4629; *ibid.*, 1985, **107**, 8294.

5 I. Ojima and T. Kogure, *Organometallics*, 1982, **1**, 1390; I. Ojima, T. Kogure, M. Nihonyanagi, and Y. Nagai, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 3506; M. F. Semmelhack and R. N. Misra, *J. Org., Chem.*, 1982, **47**, 2469.

6 C. L. Frye, *J. Am. Chem. Soc.*, 1964, **86**, 3170; F. P. Boer, J. J. Flynn, and J. W. Turley, *ibid.*, 1968, **90**, 6973.

7 K. Tamao, T. Kakui, and M. Kumada, *J. Am. Chem. Soc.*, 1978, **100**, 2268; K. Tamao, J. Yoshida, and M. Kumada, *J. Synth. Org. Chem., Jpn.*, 1980, **38**, 769 and references cited therein.

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† The reduction of carbonyl compounds using trichlorosilane–dilithium pyrocatecholate in tetrahydrofuran has recently appeared; see K. Sato, M. Kira, and H. Sakurai, the 52nd Spring Annual Meeting of Chemical Society of Japan, 1W46, Kyoto, April 1—4, 1986. We are grateful to Professor Sakurai of Tohoku University for information prior to publication.

In addition to the *cis* selectivity with 2-methylcyclohexanone, a considerable amount of *cis*-alcohol (*cis* : *trans* = 32 : 68) was obtained from 4-t-butylcyclohexanone in contrast with the fluoride ion-promoted reaction (18 : 82) which proceeds *via* the pentaco-ordinate silicon hydride (ref. 4). These results are consistent with the fact that the *cis* selectivity becomes higher with increasing steric bulk of the hydride reagent; see D. C. Wigfield, *Tetrahedron*, 1979, **35**, 449 and references cited therein.