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Radical Reactions in Aqueous Medium Using $(Me_3Si)_3SiH$

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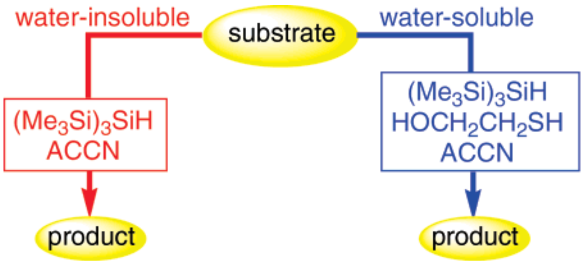
ABSTRACT



$(Me_3Si)_3SiH$ was used as a successful reagent in a variety of radical-based transformations in water. The system comprising substrate, silane, and initiator (ACCN) mixed in aqueous medium at 100 °C worked well for both hydrophilic and hydrophobic substrates, with the only variation that an amphiphilic thiol was also needed in case of the water-soluble compounds.

The motivation to use water as solvent for organic reactions is not only because it is a cheap, safe, and an environmentally friendly substitute for organic solvents but also because it often increases reaction rate and selectivity.[1−3] Indeed, a further encouragement for the use of this solvent came from the concept of the reactivity “on water”, introduced by Sharpless and co-workers to describe reactions of organic substances that are not water soluble but yet react well or even considerably faster in the presence of water than in organic solvents.[4] Another advantage is connected to the workup, with the organic and aqueous phases that separate, thus eliminating the need for complex isolation steps to obtain the product.

Radical chemistry was also performed in water with some success in functional group transformations and C−C bond formation.[5,6] These reactions can be divided into three categories: (i) Et_3B-induced halogen atom transfer radical additions (intra- or intermolecular),[7] (ii) water-soluble reducing agents,[6b,c] such as $R_2P(O)H$ or ad hoc synthesized group 14 hydride,[8] and (iii) water-insoluble reducing agents that are stable to hydrolysis.[9,10] For example, some water-compatible reagents have been proposed, such as tri-2-

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(1) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095−3165.

(2) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751−2772.

(3) Grieco, P. A., Ed. *Organic Synthesis in Water*; Blackie Academic and Professional: London, 1998.

(4) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275−3279.

(5) For a review, see: Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **2002**, 674−686. Also see: Renaud, P., Sibi, M. P., Eds. *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, 2001; Vol. 1.

(6) For recent selected papers, see: (a) Campaña, A. G.; Estévez, R. E.; Fuentes, N.; Robles, R.; Cuerva, J. M.; Buñuel, E.; Cárdenas, D. J.; Oltra, J. E. *Org. Lett.* **2007**, *9*, 2195−2198. (b) Cuerva, J. M.; Campaña, A. G.; Justicia, J.; Rosales, A.; Oller-López, J. L.; Robles, R.; Cárdenas, D. J.; Buñuel, E.; Oltra, J. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 5522−5526. (c) Cho, D. H.; Jang, D. O. *Synlett* **2005**, 59−62. (d) Khan, T. A.; Tripoli, R.; Crawford, J. J.; Martin, C. G.; Murphy, J. A. *Org. Lett.* 2**003**, *5*, 2971−2974. (e) Suárez, R. M.; Sestelo, J. P.; Sarandeses, L. A. *Chem. Eur. J.* **2003**, *9*, 4179−4187.

(7) (a) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 11041−11047. (b) Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 7776−7785.

(8) (a) Light, J.; Breslow, R. *Tetrahedron Lett.* **1990**, *31*, 2957−2960. (b) Rai, R.; Collum, D. B. *Tetrahedron Lett.* **1994**, *35*, 6221−6224. (c) Yamazaki, O.; Togo, H.; Matsubayashi, S.; Yokoyama, M. *Tetrahedron* **1999**, *55*, 3735−3747.

(9) (a) Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2002**, *74*, 747−752. (b) Yorimitsu, H.; Oshima, K. *Inorg. Chem. Commun.* **2005**, *8*, 131−142.

(10) Postigo, A.; Ferreri, C.; Navacchia, M. L.; Chatgilialoglu, C. *Synlett* **2005**, 2854−2856.

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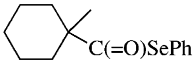
furylgermane, that is not soluble but effective in the transformation of both hydrophobic and hydrophilic organic halides.[9] Analogously, we reported that the reduction of a few organic iodides and bromides proceeds well with $(TMS)_3SiH$ (TMS = Me_3Si), and the immiscibility of this reagent with water does not influence the reactivity.[10]

The proposal of $(TMS)_3SiH$ in water can be attractive from the point of view of its commercial availability and stability to aqueous, pH, and oxidative conditions in addition to its optimal environmental compatibility. In the present paper two methods are reported for the use of $(TMS)_3SiH$ in water, depending on the hydrophilic or hydrophobic character of substrates.[11] Our findings extend the use of the silicon reagent for simple, convenient, and safe radical reactions in water, thus providing more reasons for abandoning a tradition-based choice of organic solvents in routine chemical transformations.

Reduction of water-insoluble compounds. A heterogeneous mixture of substrate (0.05 mmol), $(TMS)_3SiH$ (1.2−2.0 equiv), 1,1′-azobis(cyclohexane-carbonitrile) (ACCN; 0.3 equiv), and 5 mL of water was flushed by Ar for 10 min before heating at 100 °C for 4 h.[12] After the elapsed reaction time, addition of hexane, and extraction, the organic phase was analyzed using authentic compounds as references. All reactions proceeded in good yields (Table 1). The removal of bromine and iodine proceeded smoothly. The removal of PhSe afforded methylcyclohexane, indicating that the decarbonylation of acyl radicals takes place. The efficiency of deoxygenation of alcohols (Barton−McCombie reaction) is independent of the type of thiocarbonyl derivative (e.g., *O*-arylthiocarbonate, *O*-thioxocarbamate, thiocarbonyl imidazole, or xanthate), as previously reported for $(TMS)_3SiH$ in organic solvents.[11]

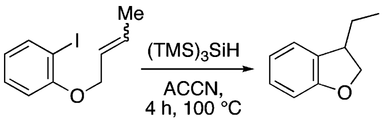
Table 1. Reduction of Water-Insoluble Compounds in Water

$$\mathrm{RX} \xrightarrow[\text{ACCN (0.3 equiv)}]{(\mathrm{TMS})_3\mathrm{SiH}\ \text{(1.2 - 2.0 equiv)}} \mathrm{RH}$$

RX[a]	RH, yield %
n-$C_{16}H_{33}Br$	97
1-Iodoadamantane	91
 C(=O)SePh	83
c-$C_{12}H_{23}OC(=S)OPh$	89
c-$C_{12}H_{23}OC(=S)NHPh$	85
c-$C_{12}H_{23}OC(=S)Im$	90
c-$C_{12}H_{23}OC(=S)SMe$	98

[a] Conditions: substrate (0.05 mmol), 4 h, 100 °C.

The reaction conditions were also applied for a radical cyclization of the 1-allyloxy-2-iodobenzene derivative **1** as shown in eq 1. The result was satisfactory, with a 85% yield of the cyclized product **2**.[13]

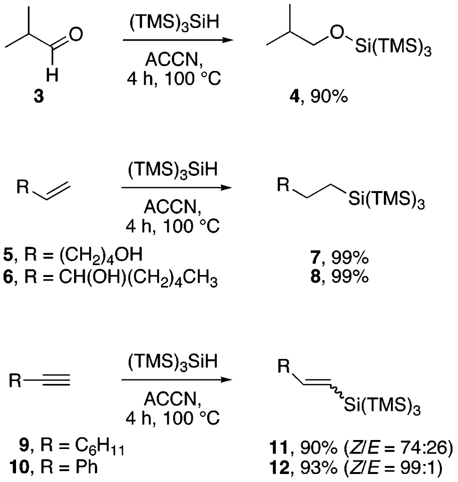


(1)

1 **2**, 85%

We next performed the hydrosilylation of unsaturated bonds, using different hydrophobic compounds, such as aldehydes (**3**),[14] alkenes (**5** and **6**),[15] and alkynes (**9** and **10**)[15,16] under the same reaction conditions (Scheme 1). Again, the efficiency of the reaction was very good, and in all cases good to quantitative formation of the hydrosilylation products was achieved. It is worth mentioning the higher *cis* stereoselectivity observed in water vs toluene (e.g., *Z*/*E* = 51:49 for **11** and 84:16 for **12** in toluene at 90 °C).

Scheme 1. Hydrosilylation of Water-Insoluble Compounds in Water



These results show that the nature of the reaction medium does not play an important role either in influencing the efficiency of the radical transformation or in the ability to dissolve the reagents. It can be deduced that all water-insoluble materials (substrate, reagents, and initiator) suspended in the aqueous medium can interact, due to the vigorous stirring that creates an efficient vortex and dispersion. Probably the radical initiation benefits from the

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[11] For reviews of $(TMS)_3SiH$ in organic synthesis, see: (a) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188−194. (b) Chatgilialoglu, C.; Ferreri, C.; Gimisis, T. In *The Chemistry of Organic Silicon Compounds*; Rappoport, Z., Apeloig, Y., Eds.; Wiley: Chichester, 1998; Vol 2, Chapter 25, pp 1539−1579. (c) Chatgilialoglu, C. *Organosilanes in Radical Chemistry*; Wiley: Chichester, 2004.

[12] The water-insoluble radical initiator 1,1′-azobis(cyclohexane-carbonitrile) (ACCN; half-life of 2.33 h at 100 °C) was found to give the best performance for both hydrophobic and hydrophilic substrates.

[13] Curran, D. P.; Totleben, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 6050−6058.

[14] Kulicke, K. J.; Giese, B. *Synlett* **1990**, 91−92.

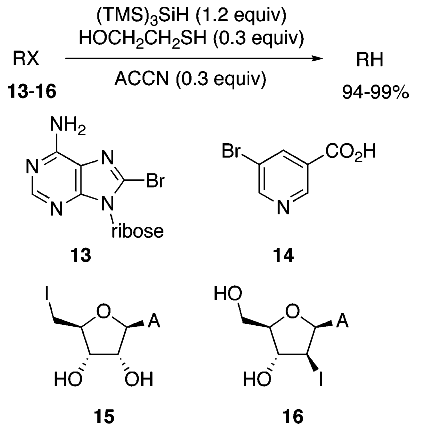
[15] Kopping, B.; Chatgilialoglu, C.; Zehnder, M.; Giese, B. *J. Org. Chem.* **1992**, *57*, 3994−4000.

[16] Miura, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2356−2364.

enhanced contact surface of tiny drops containing $(TMS)_3SiH$ and ACCN.

Reduction of water-soluble compounds. When the above-mentioned reaction conditions were used for the reduction of water-soluble compounds, no reaction or very low conversions were observed. We addressed our attention to the $(TMS)_3SiH/RSH$ reducing system, using the amphiphilic 2-mercaptoethanol ($HOCH_2CH_2SH$) as the thiol.[17−19] This amphiphilic thiol is successfully used for radical reactions in the heterogeneous system of vesicle suspensions.[20] Excellent results were achieved by adding this amphiphilic thiol to the system. A heterogeneous aqueous mixture of water-soluble starting material (10 mM), $(TMS)_3SiH$ (1.2 equiv), $HOCH_2CH_2SH$ (0.3 equiv), and ACCN (0.3 equiv) was flushed by Ar for 10 min before heating at 100 °C for 4 h. After the elapsed reaction time, addition of hexane, and extraction, the water phase was analyzed using authentic compounds as references. The reduction of hydrophilic substrates in water has the additional advantage of an easy separation of the silane byproducts by partition between water and organic phases. Few representative bromides and iodides were reduced in excellent yields as reported in Table 2.

Table 2. Reduction of Water-Soluble Halides in Water



13 **14** **15** **16**

RX[a]	convn (%)	RH, yield[b] (%)
13	>99	94
14	80	95
15	>99	99
16	98	99

[a] Conditions: substrate (10 mM), 4 h, 100 °C. [b] Based on converted substrate.

Scheme 2. Propagation Steps for the Reduction of Water-Soluble Halides

$$R^\bullet + HOCH_2CH_2SH \longrightarrow RH + HOCH_2CH_2S^\bullet$$

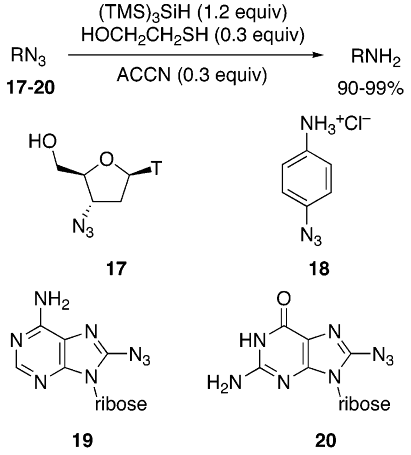
$$HOCH_2CH_2S^\bullet + (TMS)_3SiH \rightleftharpoons HOCH_2CH_2SH + (TMS)_3Si^\bullet$$

$$(TMS)_3Si^\bullet + RX \longrightarrow (TMS)_3SiX + R^\bullet$$

The reduction of an organic halide (RX) by the couple $(TMS)_3SiH/$ $HOCH_2CH_2SH$ under radical conditions can occur following the propagation steps in Scheme 2; that is, the alkyl or aryl radicals ($R^\bullet$) abstract hydrogen from the thiol in the water phase, and the resulting thiyl radicals migrate into lipophilic dispersion of the silane and abstract a hydrogen atom, thus regenerating the thiol along with the chain-carrying silyl radical for a given RX. The reaction of silyl radical with halide is expected to occur at the interface of the organic dispersion with the aqueous phase. It is worth mentioning that the reaction of thiyl radical with silane is estimated to be exothermic by ca. -3.5 kcal mol^{-1}.[18]

Another successful class of radical reductions in water has been obtained by the transformation of azides to primary amines under the same experimental conditions. The results are reported in Table 3. Again no reaction was observed in the absence of the amphiphilic 2-mercaptoethanol.

Table 3. Reduction of Water-Soluble Azides in Water



17 **18** **19** **20**

RN3[a]	convn (%)	RNH2, yield[b] (%)
17	70	99
18	>99	90
19	>99	95
20	>99	90

[a] Conditions: substrate (10 mM), 4 h, 100 °C. [b] Based on converted substrate.

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(17) The $(TMS)_3SiH/RSH$ reducing system has recently been tested using the well-known *free-radical-clock* methodology and allowed the determination of a large number of rate constants for the reactions of carbon-centered radicals with thiols.[18]

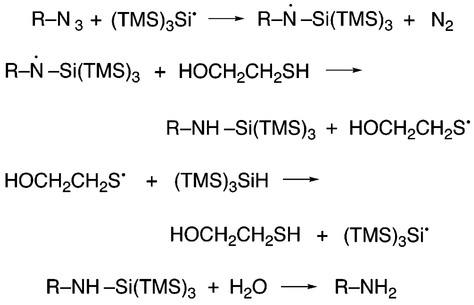
(18) Chatgilialoglu, C. *Helv. Chim. Acta* **2006**, *89*, 2387−2398.

(19) For a review on the Et_3SiH/RSH reducing system in organic solvents, see: Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25−35.

(20) Chatgilialoglu, C.; Ferreri, C.; Mulazzani, Q. G.; Ballestri, M.; Landi, L. *J. Am. Chem. Soc.* **2000**, *122*, 4593−4601. Ferreri, C.; Costantino, C.; Perrotta, L.; Landi, L.; Mulazzani, Q. G.; Chatgilialoglu, C. *J. Am. Chem. Soc.* **2001**, *123*, 4459−4468. Ferreri, C.; Samadi, A.; Sassatelli, F.; Landi, L.; Chatgilialoglu, C. *J. Am. Chem. Soc.* **2004**, *126*, 1063−1072.

(21) Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G. *J. Org. Chem.* **2006**, *71*, 5822−5825.

Scheme 3. Reaction Mechanism for the Reduction of Water-Soluble Azides



$$R{-}N_3 + (TMS)_3Si^{\bullet} \longrightarrow R{-}\dot{N}{-}Si(TMS)_3 + N_2$$

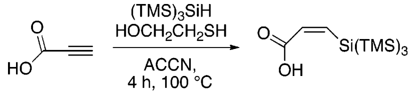
$$R{-}\dot{N}{-}Si(TMS)_3 + HOCH_2CH_2SH \longrightarrow R{-}NH{-}Si(TMS)_3 + HOCH_2CH_2S^{\bullet}$$

$$HOCH_2CH_2S^{\bullet} + (TMS)_3SiH \longrightarrow HOCH_2CH_2SH + (TMS)_3Si^{\bullet}$$

$$R{-}NH{-}Si(TMS)_3 + H_2O \longrightarrow R{-}NH_2$$

The mechanistic steps of this reaction are shown in Scheme 3, in analogy with the pathways reported for the radical reduction of aromatic azides with triethylsilane in toluene,[21] with the addition of silyl radicals to the azide function, liberation of nitrogen, and formation of a silyl-substituted aminyl radical. The thiol is the hydrogen atom donor to this intermediate, and it can be regenerated by its interaction with the silane, thus carrying on the chain. The hydrolysis of the silylamine rapidly occurred in water and afforded the amine as final product.

The hydrosilylation of water-soluble propiolic acid (**21**) was also tested under the same conditions. The reaction proceeded efficiently giving the *Z*-alkene **22** with optimal yield (eq 2). It is worth noting that this hydrosilylation has been recently reported to be efficient also in neat conditions, where the initiation was linked to the presence of adventitious oxygen.[22]



(2)

21 **22**, 95%

In conclusion, the usefulness of $(TMS)_3SiH$ as a versatile radical reagent in water has been demonstrated. These results are expected to further encourage the use of the silane-mediated transformation, shifting to cheap, safe, yet efficient conditions. This new synthetic methodology should divert the routine-motivated choice for reaction conditions in different fields, such as medicinal chemistry, where the good enviromental impact and absence of toxicity renders water the best option for solvent medium.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[22] Liu, Y.; Yamazaki, S.; Yamabe, S. *J. Org. Chem.* **2005**, *70*, 556–561.