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The Radical-Based Reduction with $(TMS)_3SiH$ 'On Water'

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This paper is dedicated to the memory of Dr. Anne Ghosez-Giese. Her smile and gentle spirit is greatly missed.

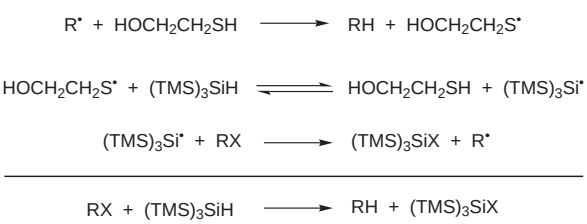
Abstract: Reduction of different organohalides, bromonucleosides among them, was successfully carried out in yields ranging from 75% to quantitative, using $(TMS)_3SiH$ in a heterogeneous system with water as the solvent. Our procedure, employing 2-mercaptoethanol as the catalyst and the hydrophobic diazo-compound ACCN as the initiator, illustrates that $(TMS)_3SiH$ can be the radical-based reducing agent of choice in aqueous medium. $(TMS)_3SiH$ does not suffer from any significant reaction with water and can safely be used with additional benefit, such as ease of purification and environmental compatibility.

Key words: radical reactions, reductions, tris(trimethylsilyl)silane, azo compounds, thiols

During the past few decades, a number of organic reactions have been successfully performed in water. This solvent appears to be not merely an environmentally friendly alternative, which results in considerable money saving on the industrial scale, ease of purification and better safety conditions, but it has also significant additional advantages. It increases rate and selectivity, as for example in the case of concerted reactions such as Diels–Alder reactions,[2] Mukaiyama aldol reaction,[3] and Sharpless' 'click' chemistry.[4] However, the solubility of reactants was a determining and governing factor in choosing reaction conditions for organic syntheses. Therefore, the poor water solubility of many organic reactants was seen as a major problem in the affirmation of the aqueous methodology, which could be partially solved by the use of additives and surfactants with hydrophobic substrates.[5]

Synthetically useful radical reactions in aqueous media are far from being achieved.[6] However, ad hoc synthesized water-soluble group 14 hydrides have been used for the reduction of halides[7] or Et_3B-induced atom transfer cyclization and addition of halogenated compounds to alkenes.[8] Hydrophobic substrates limit the scope of these reactions. In our laboratory, unconventional but high yield methods have been used in aqueous solution or suspension to synthesize some biologically relevant products, such as 5′,8-cyclo-2′-deoxyadenosine[9] and *trans*-phospholipids.[10]

Recently, the scenario has changed and immiscibility has started to be considered advantageous. The chemical reactions 'on water' are now regarded with a great attention,[11] since the reactivity in suspension obtained by vigorous stirring of immiscible reactants seems to benefit from the enhanced contact surface of the resulting tiny drops, as well as from the unique molecular properties developed at the interface between water and hydrophobic phases. The reported methodology of polarity-reversal catalysis attracted our attention,[12,13] since the thiol/silane couple shows not only an efficient synergy of radical production and regeneration, but could also provide for the use of an amphiphilic thiol, in order to enhance the radical reactivity at the interface. For the reduction of an organic halide (RX) by the couple $(TMS)_3SiH/HOCH_2CH_2SH$ under radical conditions, the propagation steps in Scheme 1 are expected. That is, the alkyl radicals abstract hydrogen from the thiol and the resulting thiyl radicals abstract hydrogen from the silane, so that the thiol is regenerated along with the chain-carrying silyl radical for a given RX.



Scheme 1

This paper reports the first data on the application of the couple $(TMS)_3SiH/HOCH_2CH_2SH$ for effecting radical reductions in water and the different results achieved with hydrophobic and hydrophilic initiators.

We initially tested the stability of $(TMS)_3SiH$ in water by dissolving the reagent in a THF–water (4:1) mixture and following our standard reaction conditions (i.e., 100 °C, 4 h, Ar-deoxygenated). GC and GC-MS analyses of the hexane extracts showed that the yield of $(TMS)_3SiH$ is ca. 95%, with no observation of degradation products. This indicated that $(TMS)_3SiH$ does not suffer any significant reaction with the medium and can safely be used as an efficient reducing agent in water as will be shown below.

The reduction reactions proceeded smoothly in yields ranging from quantitative to high (Table 1).[14] All yields were optimized in terms of initiator selection and concentration, and 2-mercaptoethanol and $(TMS)_3SiH$ concentrations. Entries 1 and 2 show the reduction of hydrophobic 4-iodobutyric acid and hydrophilic 5-iodouracil, affording the corresponding reduced products in

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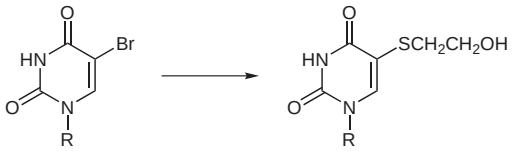
yields >90%. Both 2,2′-azobis(2-amidinopropane) dihydrochloride (AAPH, water-soluble) and 1,1′-azobis(cyclohexanecarbonitrile) (ACCN, organic solvent soluble) are good initiators for these reactions. The half-life of ACCN at 100 °C is 2.33 hours, while that of AAPH is ca. 1.1 hours at 73 °C.

The reductions of hydrophilic (1*S*)-bromocamphor-10-sulfonic acid and 5-bromouridine under similar conditions were also considered (entries 3 and 4). Using water-soluble AAPH initiator no reaction occurred for the camphor derivative, whereas 5-bromouridine afforded only compound **1** in 82% yield (based on 17% converted substrate, Equation 1). The same compound was obtained in the absence of $(TMS)_3SiH$ suggesting that the thiyl radical undergoes an *ipso*-substitution with ejection of bromine atom as the key step in this radical chain reaction. However, when 3 mM ACCN is used as initiator, both substrates afforded 90% yield of the corresponding reduction products, although the conversions of starting material were as low as 10%. By increasing the amount of ACCN, however, the disappearance of starting material increased in favor of the reduction product. In fact, a dependence of the reduction product formation upon initiator concentration was found as shown in Figure 1. A blank experiment, employing one equivalent of 5-bromouridine, two equivalents of initiator, in the absence of $(TMS)_3SiH$, afforded the reduced product uridine in traces, showing that ACCN alone cannot act as the reducing agent.



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Equation 1

We next focused on the relevance and role of 2-mercaptoethanol in the reduction process. We performed a series of experiments of 5-bromouridine with $(TMS)_3SiH$ in water, using ACCN as initiator and varying the amount of the thiol (Table 2). In the absence of 2-mercaptoethanol, the reaction became very sluggish, with poor reduction yields (entry 1). However, high amounts of 2-mercaptoethanol did not increase yields substantially (entries 3 and 4), indicating the catalytic role of this amphiphilic thiol. In these runs, we managed to find optimal reaction conditions for the reduction of 5-bromouridine, employing the following ratios of reactants: [substrate]/[$(TMS)_3SiH$] = 0.85; [substrate]/[ACCN] = 0.55; and [substrate]/[$HOCH_2CH_2SH$] = 3–3.5.

We also subjected 8-bromoadenosine and 8-bromoguanosine to reduction with $(TMS)_3SiH/HOCH_2CH_2SH$ in water (Table 1, entries 5 and 6). As in the case of other

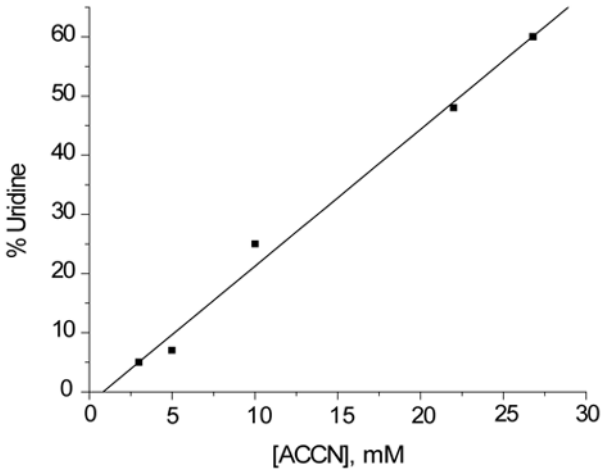

Figure 1 Yield (%) of uridine vs. ACCN concentration. The reduction reactions were carried out by vigorous stirring of the mixture of 5-bromouridine (10 mM), $(TMS)_3SiH$ (12 mM), 2-mercaptoethanol (2.85 mM), varying amounts of ACCN, and H_2O (5 mL) at 100 °C in 5-mL screw-cap Wheaton vials equipped with Mininert valve for 4 h (or otherwise indicated). All solutions were deoxygenated with a stream of Ar for 10 min prior to addition of initiator.

bromides, ACCN was found to be the initiator of choice despite not being water-soluble. Of note is the fact that these substrates, unlike 5-bromouridine, do not require large amounts of initiator to achieve good reduction yields. Three decimal equivalents of initiator are needed to attain reduction. However, much better yields of reduced products are obtained when we added triethylamine to the reaction medium (preventing deglycosylation) and discriminated the reaction times for the two purine nucleosides (1 h for 8-bromoadenosine and 9 h for 8-bromoguanosine).

The reduced compounds can be isolated from the reaction mixtures by a facile extraction into hexane, removing the excess of $(TMS)_3SiH$ and its by-products. In some cases the reduction reactions afforded products pure enough for proper characterization. Column chromatography on reverse-phase silica gel afforded the reduced compounds in high purity.

In summary, we demonstrated that $(TMS)_3SiH$ together with catalytic amounts of 2-mercaptoethanol and ACCN as initiator can be used as a reducing system in water for a variety of organic halides. AAPH could be expected to be a better initiator than ACCN, due to solubility concerns on the latter. However, our results show the opposite. We suggest that the radical initiation benefits from the enhanced contact surface of tiny drops containing $(TMS)_3SiH$ and ACCN obtained in the vigorously-stirred aqueous suspension. Studies on the dependence of some reduction yields upon initiator concentration and further applicability of the system 'on water' are under investigation in our laboratory.

Table 1 Reduction of Organic Halides (10 mM) with $(TMS)_3SiH$ (12 mM) and $HOCH_2CH_2SH$ (2.85 mM) in Water

Entry	Substrate	Initiator (mM)	Temp (°C)[a]	Yield (%)[b]
1	4-Iodobutyric acid	APPH, 3	73	99
		ACCN, 3	100	100
2	5-Iodouracil	APPH, 3	73	90[c]
		ACCN, 3	100	98[d]
3	(1*S*)-Bromocamphor-10-sulfonic acid	APPH, 3	73	–
		ACCN, 3	100	90[e]
		ACCN, 33	100	95
4	5-Bromouridine	APPH, 3	73	–[f]
		ACCN, 3	100	90[e]
		ACCN, 15.4	100	90[g]
5	8-Bromoadenosine	APPH, 3	73	–
		ACCN, 3	100	94[h]
6	8-Bromoguanosine	APPH, 3	73	–
		ACCN, 3	100	75[i]

[a] Reaction time 4 h or otherwise indicated.
[b] Yields are based on the consumed substrate, the consumption being higher than 95% or otherwise indicated.
[c] Based on 65% converted substrate.
[d] Based on 81% converted substrate.
[e] Based on 10% converted substrate.
[f] Converted substrate: 17%; no reduction product; 14% yield of compound **1**.
[g] Together with 10% yield of compound **1**; overnight reaction.
[h] In presence of 3 equiv of Et_3N; the reaction is over after 1 h.
[i] In presence of 3 equiv of Et_3N; the yield of guanosine was monitored vs. time, the reported yield was after 9 h.

Table 2 Reduction of 5-Bromouridine (ca.10 mM) with $(TMS)_3SiH$ (12 mM)/$HOCH_2CH_2SH$ (Varying Amounts) in Water at 100 °C Using ACCN (23–27 mM) as Initiator

Entry	Thiol (mM)	Conversion (%)	Uridine (%)	Adduct (%)[a]
1	0	50	25	–
2	2.85	73	60	9
3	5.7	89	75	11
4	10	85	70	11

[a] Compound **1**, see text.

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(13) Chatgilialoglu, C. *Organosilanes in Radical Chemistry*; Wiley: Chichester, **2004**.
(14) **General Experimental Procedure.**
In a 5-mL screw-cap Wheaton vial equipped with a magnetic stirrer, a heterogeneous mixture of halogenated substrate (0.05 mmol, 10 mM), tris(trimethylsilyl)silane (18.5 μL, 0.06 mmol, 12 mM) and 2-mercaptoethanol (1 μL, 0.014 mmol, 2.85 mM) was prepared in H_2O (0.5 mL). The mixture was deoxygenated with a slow stream of argon for 10 min. The initiator was added and the vial was placed in a thermostatically controlled metal rack at the desired temperature (see Table 1). The reaction was monitored by HPLC analysis at different times, and the products were recognized by comparison with commercial references. For product isolation, after extraction by *n*-hexane, the aqueous phase contained the reduced product, which can be further purified by reverse-phase column chromatography. The procedure was also performed on a 10-fold scale with similar results.