Safe, facile radical-based reduction and hydrosilylation reactions in a microreactor using tris(trimethylsilyl)silane

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A highly efficient system for tris(trimethylsilyl)silane (TTMSS) mediated deoxygenation, dehalogenation and hydrosilylation reactions is described in a microstructured device; this convenient platform enables the scale up of radical-based processes.

Microstructured continuous-flow reactors and chip based microreactors are becoming increasingly popular to overcome hurdles associated with the use of batch reactors in synthetic chemistry.[1] Traditional batch methods have inherent limitations regarding the optimisation of reaction conditions and scale-up. The small internal dimensions of microreactors require minimal amounts of reagent that are processed under precisely controlled conditions. Subsequently, rapid reaction screening is possible while overall process safety is improved. In addition, reactions can be conducted at elevated temperatures and under pressures which are not accessible using conventional flasks.[2] Subsequently, reactions that have previously been considered to be unattractive on large scale for practical and/or safety reasons are now within the reach of process chemists.[3]

Radical reduction reactions such as deoxygenations and dehalogenations are important synthetic transformations.[4] In particular, free radical based reactions such as Barton–McCombie deoxygenations[5] and dehalogenations have received considerable attention due to their versatility and functional group tolerance.[6] Furthermore, development of tris(trimethylsilyl)silane (TTMSS) as an efficient, non-toxic alternative to tin hydrides as the reducing agent in radical-based reductions has overcome many of the drawbacks associated with these processes.[7] Herein, we report the use of TTMSS as the reducing reagent in continuous-flow microreactors for radical-based transformations.

Microreactors enable rapid and efficient heat control, solvent superheating, and high pressures, features that are advantageous in conducting free radical deoxygenations and dehalogenations. For this study a glass-chip microreactor with an internal volume of 1.0 mL was employed (Fig. 1).[8] Reagents were introduced separately *via* two inlets using a syringe pump (Harvard, PHD 22/2000 with multi-syringe rack).

The TTMSS-mediated reduction of various alcohol-derived thiocarbonyl derivatives was performed in a microstructured device at 130 °C with 5 min residence time. Following an initial solvent screen, toluene was identified as the solvent of choice. Superheating to 130 °C to effect the desired reaction was possible using a simple backpressure valve thereby avoiding the use of conventional toxic or chlorinated solvents (*e.g.* CCl_4 or benzene).

Initial reductions were performed on the xanthate and imidazolylthiocarbamate derivatives of dodecanol (entries 1 and 2, respectively, Table 1) to furnish the parent alkane in excellent yield. Furthermore, the related chloro-substituted xanthate was chemoselectively reduced to 1-chlorodecane in 70% yield (entry 3).

To investigate the scope and applicability of this method to the synthesis of biologically and industrially relevant small molecules, the preparation of deoxy sugars was examined. The deoxygenation of the diacetone-D-glucose derivative to the corresponding ribohexofuranose (entry 4) proceeded in excellent yield; a process that offers considerable advantages in operational simplicity compared to the literature procedure.[9] The preparation of protected 6-deoxy-D-galactose from the corresponding primary dithiocarbonate also proceeded in >90% yield (entry 5). More sterically demanding systems such as the secondary C3 dithiocarbonate of dihydrocholesterol were also readily tolerated to furnish the reduced product in 80% yield, and the tertiary carbinol derivative of adamantane was processed to the parent hydrocarbon in excellent yield.

Encouraged by these results, we embarked on a comparative study to explore the radical-based reduction of a variety of structurally related halides.[10] Iodo-, bromo- and chloro-dodecanol proved to be excellent substrates for this reaction system yielding dodecanol in excellent yields (85, 83 and 67% yields, respectively, entries 8, 9 and 10). Similarly, bromoadamantane was cleanly dehalogenated in 86% yield (entry 11). Interestingly, the conversion of the iodo-derivatives of galactose and glucose to the corresponding deoxy-sugars (entries 12 and 13) proceeded in >90% yield; results that compare favourably with the deoxygenation reactions of the corresponding thiocarbonate derivatives (entries 4 and 5). Finally, the scope of this dehalogenation process was extended to include aromatic bromides such as 9-bromophenanthrene (entry 14). The efficiency of the reduction of this substrate showed slight concentration dependence. However, after a

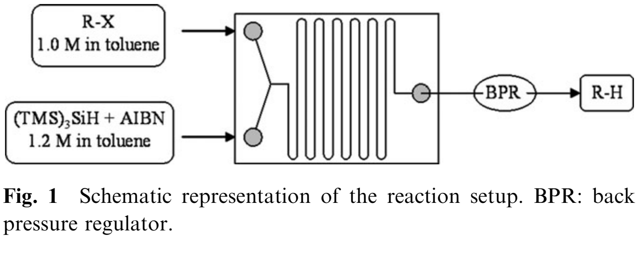

Fig. 1 Schematic representation of the reaction setup. BPR: back pressure regulator.

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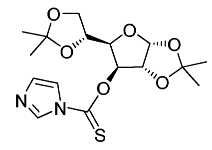
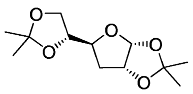
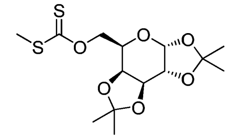
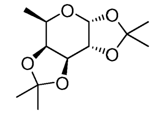
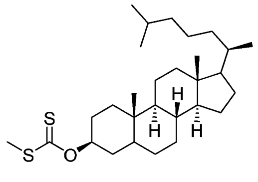
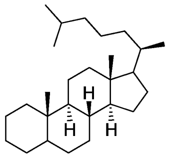
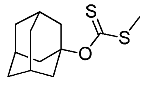
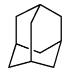
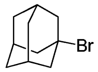
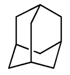
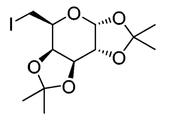
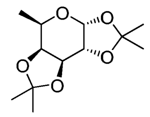
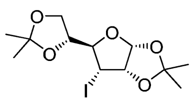
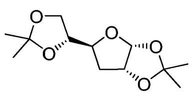
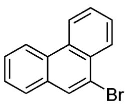
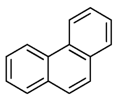
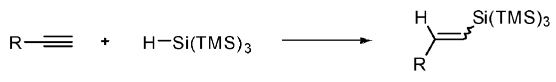
Table 1 TTMSS mediated deoxygenations and dehalogenations of various substrates in continuous flow

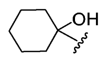
Entry	Substrate[a]	Product	Yield[b] (%)
1	n-$\mathrm{C_{12}H_{25}OC(S)SMe}$	n-$\mathrm{C_{12}H_{26}}$	89
2	n-$\mathrm{C_{12}H_{25}OC(S)Im}$	n-$\mathrm{C_{12}H_{26}}$	94
3	$\mathrm{ClC_{10}H_{20}OC(S)SMe}$	n-$\mathrm{C_{10}H_{21}Cl}$	70
4			92
5			93
6			85
7			77
8	n-$\mathrm{C_{12}H_{25}I}$	n-$\mathrm{C_{12}H_{26}}$	85
9	n-$\mathrm{C_{12}H_{25}Br}$	n-$\mathrm{C_{12}H_{26}}$	83
10	n-$\mathrm{C_{12}H_{25}Cl}$	n-$\mathrm{C_{12}H_{26}}$	67[c]
11			86
12			98
13			93
14			92[d,e]

[a] A solution of the substrate (1.0 mol dm^{-3} in toluene) and TTMSS (1.2 equiv.) and 10 mol% of AIBN (10 mol%) in toluene were simultaneously injected into microreactor preheated at 130 °C for 5 min of residence time. [b] Isolated yield unless otherwise stated. [c] Conversion in percentage as measured by ^{1}H NMR spectroscopy. [d] A solution of 9-bromophenanthrene (1.0 mol dm^{-3} in toluene), TTMS (1.2 equiv.) and AIBN (10 mol%) were premixed and injected through a single inlet. [e] Based on 93% conversion.

facile optimisation process, phenanthrene was reproducibly formed in >90% yield.

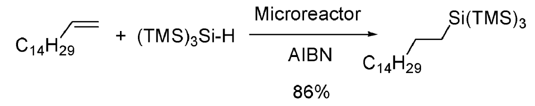
Table 2 Hydrosilylation of selected alkynes in a microreactor



Entry	R	*Z* : *E* ratio[a]	Yield[b] (%)
1	Ph	98 : 2 (84 : 16)[c]	96 (88)[c]
2	n-$\mathrm{C_6H_{13}}$	77 : 23	91
3		11 : 89	94

[a] A mixture of the alkyne in toluene (1.0 mol dm^{-3}), TTMS (1.2 equiv.) and AIBN (10 mol%) were injected trough a single inlet with a flow rate of 200 μL min^{-1}; *Z* : *E* ratio determined by ^{1}H NMR spectroscopy. [b] Isolated yield. [c] Literature values (see ref. 11).

Gratifyingly, the use of tris(trimethylsilyl)silane (TTMSS) in microreactor-based Barton–McCombie deoxygenation and dehalogenation reactions appears to general, and led us to explore additional transformations using this reagent. The TTMSS adds in a highly regioselective manner across a range of alkenes and alkynes by a free-radical chain mechanism to form silanes and vinyl silanes, respectively.[11] It was envisaged that the improved heat and mass transfer inherent to microreactors might have an effect on the *cis*/*trans* selectivities in the hydrosilylation reaction of alkynes while reducing reaction times. To explore this concept, a premixed solution of phenylacetylene (1.0 mol dm^{-3} in toluene), TTMSS (1.2 equiv.) and AIBN (0.1 equiv.) was passed through the microreactor system at a flow rate of approximately 200 μL min^{-1} (residence time 5 min) at 130 °C. The expected reaction product β-silylstyrene (Table 2, entry 1) was obtained in 96% yield (*Z* : *E* ratio of 98 : 2). It is interesting to note that the microreactor-based hydrosilylation of phenylacetylene gives a superior *Z* : *E* ratio when compared with the literature batch reaction.[11] Similarly, treatment of 1-octyne with TTMS yielded the expected *anti*-Markovnikov product vinylsilane in 91% yield as a mixture of geometric isomers (*Z* : *E* = 77 : 23, entry 2). Finally, hydrosilylation of 1-ethynylcyclohexanol furnished the *E*-vinyl silane as the major reaction product in excellent yield (94%, *E* : *Z* = 89 : 11, *vide infra*).[13]

 (1)

Application of this method to effect the transformation of terminal olefins such as 1-hexadecene to the saturated silane (eqn (1)) also proved to be highly successful yielding the desired compound in 86% yield.[14]

In conclusion, we have developed a facile platform to conduct radical-based transformations in a microstructured reaction device. Reduction chemistry, namely Barton–McCombie deoxygenations and dehalogenations, has been demonstrated using TTMSS as the radical reducing agent.[12] Furthermore, the scope of radical-based microreactor processes has been expanded to include hydrosilylation reactions of alkenes and alkynes.

We thank the Swiss Federal Institute of Technology (ETH) Zurich and AstraZeneca R&D (Mölndal, Sweden) for generous financial support.

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13. Spectral data for (*E*)-1-(2-tris(trimethylsilyl)silanylvinyl)cyclohexanol (Table 2, entry 3): $\nu_{\max}/\mathrm{cm}^{-1}$ (thin film) 3375 (br), 2934, 2895, 1447, 1394, 1242 and 986; δ_H (300 MHz, $CDCl_3$): 6.15 (1H, d, J = 18.6 Hz, CH = CH), 5.79 (1H, d, J = 18.6 Hz, CH = CH), 1.71–1.60 (2H, m, CH_2), 1.59–1.41 (6H, m, 3 × CH_2), 1.39–1.12 (2H, m, CH_2) and 0.16 (27H, s, 9 × Si–CH_3); δ_C (75 MHz, $CDCl_3$): 155.2, 116.9, 73.0, 37.9, 25.6, 22.3 and 0.9; HRMS calc. for $C_{17}H_{40}OSi_4$-TMS, 299.1683: found 299.1678.
14. Spectral data for 1-(tris(trimethysilyl)silanyl)hexadecane (eqn (1)): $\nu_{\max}/\mathrm{cm}^{-1}$ (thin film) 2892, 2854, 1466, 1244 and 834; δ_H (300 MHz, $CDCl_3$): 1.38–1.22 (28H, m, 14 × CH_2), 0.89 (3H, t, J = 6.4 Hz, CH_3), 0.79–0.73 (2H, m, CH_2) and 0.17 (27H, s, 9 × Si–CH_3); δ_C (75 MHz, $CDCl_3$): 34.4, 32.0, 29.8, 29.7, 29.5, 29.3, 22.8, 14.3, 7.7 and 1.3; HRMS calc. for $C_{25}H_{60}Si_4$, 472.3772: found 472.3767.