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# On the use of $(TMS)_3CH$ as novel tin-free radical reducing agent

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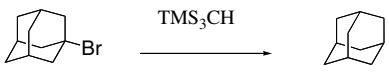
**Abstract**—$(TMS)_3CH$ is an efficient free radical reducing agent. Debromination, deiodation, dechlorination as well as decarboxylation of Barton and Kim esters can proceed smoothly using this tin-free reducing agent. Rate constants for hydrogen atom abstraction from $TMS_3CH$ by primary radicals were also determined.


Organotin hydrides such as $Bu_3SnH$, $Ph_3SnH$ and $Me_3SnH$ have successfully been used to mediate preparative radical chain processes in chemistry over the last 40 years.[1] However there are several drawbacks commonly associated with the use of these reagents in organic synthesis. Since organostannanes are toxic,[1] special handling during disposal of tin residues is necessary and often problems associated with product purification are encountered.[2] It is therefore not surprising that the so called 'tin problem' has been addressed by introducing a variety of alternative hydride sources.[3,3b,4–7] As a part of our continuing interest in the development of new reagents for use in free radical chemistry we wanted to evaluate the ability of $TMS_3CH$ to act as a free radical reducing agent. Tris(trimethylsilyl)methane ($TMS_3CH$) has several practical advantages over tributyltin hydride, for example, low toxicity, good stability and much easier work up procedure.

We chose to investigate the reduction of bromoadamantane to determine if tris(trimethylsilyl)methane ($TMS_3CH$) is an effective reducing agent under standard free radical conditions (Scheme 1). The yields were determined using GC analysis by comparison with authentic samples or by isolation of reduced product and characterization by $^1H$, $^{13}C$ NMR spectroscopy and GC analysis. In this study, reductions were carried out at substrate concentrations approximately 0.1 M, 2 equiv of $TMS_3CH$ were added at 80 °C, initiated with AIBN, VAZO® or under photolysis conditions at room temperature.[8] Reactions were carried out for 3 h and percentage of conversion determined by integration of signals corresponding to the authentic materials.[8]




**1a** **1b**

**Scheme 1.**

Table 1 lists data obtained for the reduction of bromoadamantane (**1a**) as a model compound reacting with $(TMS)_3CH$ at 80 °C in benzene (or cyclohexane) in the presence of radical initiators such as AIBN (entries 1 and 2), VAZO® (i.e., 1,1′-azobis(cyclohexanecarbonitrile))[10] (entry 3), also under photolytic initiation condition (entry 6), also in the presence of a radical inhibitor such as phenol (entry 4) as well as in the absence of AIBN (entry 5). Reaction in the presence of a stoichiometric amount of phenol, a well-known free radical inhibitor gave only very low amount (10%) of reduced product (adamantane **1b**, entry 4), confirming the free radical nature of the transformation in question.

**Table 1.** Reduction of bromoadamantane (**1a**) with $TMS_3CH$ under different conditions

| Entry | Additive | Solvent | Product | Yield (%) |
|---|---|---|---|---|
| 1 | AIBN | Benzene | **1b** | 85[a] |
| 2 | AIBN | Cyclohexane | **1b** | 80 |
| 3 | VAZO® | Benzene | **1b** | 80 |
| 4 | Phenol | Benzene | **1b** | 10 |
| 5 | None | Benzene | **1b** | 8 |
| 6 | *hv* | Benzene | **1b** | 78 |

[a] Isolated yield using procedure similar to that described in Ref. 8.

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**Table 2.** Radical reduction of various substrates with $TMS_3CH$ (2 equiv) and AIBN (0.5 equiv) in benzene

| Entry | Substrate | Product | Yield (%) |
|---|---|---|---|
| 1 | **1a** | **1b** | 85[a] |
| 2 | **1c** | **1b** | 98 |
| 3 | **1d** | **1b** | 89 |
| 4 | **2a** | **2b** | 97 |
| 5 | **2c** | **2b** | 89 |
| 6 | **3a** | **3b** | 72[a] |
| 7 | **3c** | **3b** | 80[a] |
| 8 | **3d** | **3b** | 100[a] |
| 9 | **4a** | **4b** | 100 |
| 10 | **4e** | **4b** | 100 |
| 11 | **4d** | **4c** | 70[a] |
| 12 | **4f** | **4c** | 72[a] |
| 13 | **5a** | **5b** | 86[a] |
| 14 | **6** | **7** | 72[a] |

[a] Isolated yield, reactions performed following procedure described in the Ref. 8 under the atmosphere of dry $N_2$.

Reaction in the absence of AIBN gave only very low amount (8%) of reduced product (adamantane **1b**, entry 5), highlighting once again the free radical nature of the transformation in question. Reaction under the photolytic conditions conducted at room temperature gave a high percentage of conversion (78%) to the reduced product (adamantane **1b**, entry 6) suggesting the high efficiency of the free radical transformation.

To test the scope and limitations of our new 'tin hydride' substitute, that is, $(TMS)_3CH$ as an efficient reducing agent, a series of typical radical chain defunctionalization reactions was performed using $TMS_3CH$ under conditions specified in Table 1 and results are summarized in Table 2. Primary (**3a**,**c** and **d**) (entries 6–8), secondary (**2a**) (entry 4), tertiary (**1a**) (entry 1), aromatic (**4a**,**e**) (entries 9 and 10) and benzylic (**4d**,**f**) (entries 11 and 12) halides such as chlorides, bromides or iodides were efficiently reduced in good to excellent yield under previously described conditions. Moreover, Barton–McCombie type deoxygenation reaction using xanthates (**2c**) and (**5a**) (entries 5 and 13, respectively) could be performed efficiently with $(TMS)_3CH$ on the 1.6 g scale.[9] Reactions of Barton and Kim esters (**1d** (entry 3) and **1c** (entry 2), respectively), derived from 1-adamantanecarboxylic acid also proceeded smoothly in high conversions on both GC and preparative scale[9] (Fig. 1).

Another common synthetic reaction that utilizes trialkyltin hydride is the radical cyclization reaction. Cyclization of *o*-iodophenyl allyl ether (**6**) (entry 13) could be conducted using $TMS_3CH$ as a radical reducing agent to obtain the desired cyclized product (**7**) in good isolated yield.[9] Importantly, the syringe pump technique, commonly used in free radical synthesis in order to have a control on the rate of addition and the concentration of the 'hydrogen source' present in the reaction is not necessary to conduct these transformations, which suggests that this reagent can effectively extend the 'kinetic range' available to free-radical chain systems.

In order to verify the radical nature of the transformation we determined rates of the hydrogen transfer reaction from $TMS_3CH$ to a primary radical using 5-exo-cyclization of the 5-hexenyl radical (**8**) as a radical clock (Scheme 2).[3]

Reaction of 6-bromo-1-hexene, carried out at 70 °C with AIBN (0.5 equiv) as a radical initiator, gave methylcyclopentane (**10**) and 1-hexene (**9**) as the exclusive reaction products, as determined by GC analysis. From the (**9**)/(**10**) = 0.02 ratio we could estimate the rate constant ($k_H$) for the hydrogen abstraction by the 5-hexen-1-yl radical (**8**).

Analysis of the data in Table 3 suggests that $(TMS)_3CH$ transfers a hydrogen atom at least 4 times slower than $(TMS)_3SiH$ (entries 1 and 3). In comparison to the $Bu_3SnH$ (entries 4) $(TMS)_3CH$ transfers a hydrogen atom at least 10 times slower.[11] However the $k_H$ value is significantly greater than the corresponding value for $Et_3SiH$ (entry 2) and this explains why $TMS_3CH$ can sustain the radical reaction unlike $Et_3SiH$ which cannot.

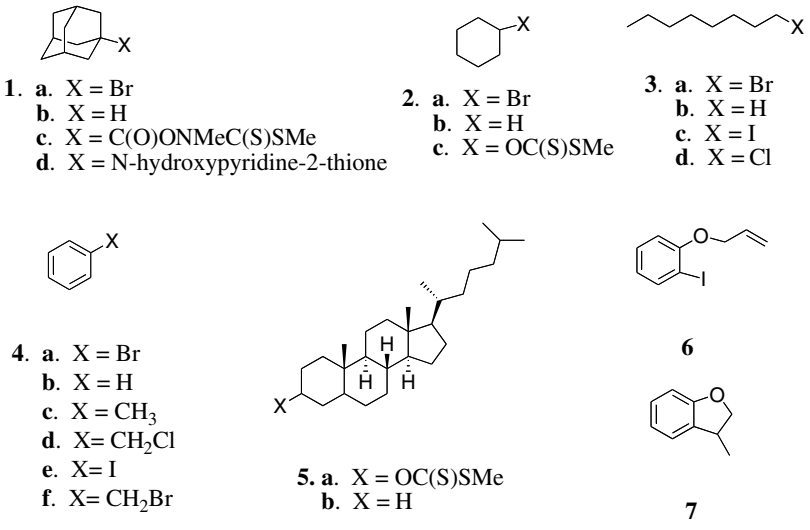
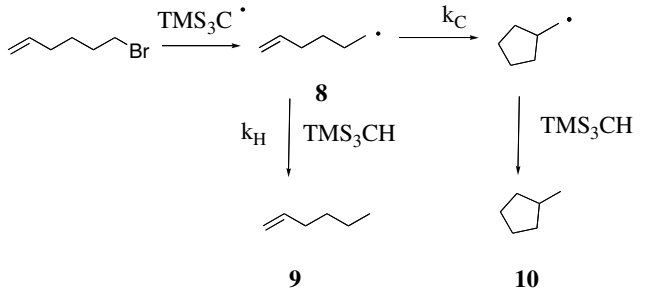



**Figure 1.**




**Scheme 2.**

**Table 3.** Rate constants for the hydrogen transfer from $TMS_3CH$ (0.09 M) to primary radical in comparison with alternative hydrogen donors at 70 °C

| Entry | H-donor | $10^{-5}\ k_H/M^{-1}\ s^{-1}$ | Reference |
|---|---|---|---|
| 1 | $(Me_3Si)_3SiH$ | 11 | 7 |
| 2 | $Et_3SiH$ | 0.04 | 10 |
| 3 | $(Me_3Si)_3CH$ | 2.5 | tw[a] |
| 4 | $Bu_3SnH$ | 24 | 11[a] |

[a] tw, Signifies this work, average of three experiments.

In summary $(TMS)_3CH$ is a highly-efficient, tin-free, radical reducing agent, which is compatible with standard radical precursor systems. Kinetic experiments as well as some preliminary computational evidence point towards $(TMS)_3CH$ being a versatile and environment friendly addition to the toolkit of organic chemists. We are currently investigating further the scope and limitations in the use of the $(TMS_3)CH$ in radical cascade reactions.

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8. Typical reduction procedure is as follows: $(TMS)_3CH$ (2 equiv) and the radical precursor (1 equiv) were dissolved in benzene (50 μL). A pyrex tube was charged with the required solution (300 μL) and AIBN (0.5 equiv) added. The solution was frozen in liquid nitrogen, sealed under vacuum and heated in the 80 °C constant temperature oil bath overnight. The reaction mixture was then analyzed by GC. Chromatography column used in investigation: trifluoroacetylated γ-cyclodextrin (Chiraldex™ G-TA 30 m × 0.25 mm) capillary column purchased from Alltech.
9. The typical procedure for the preparative scale reactions is as follows: To a solution of freshly recrystallized xantate derived from dihydrocholestane (0.1 M) in dry benzene (5 ml), tris(trimethylsilyl)methane (2 equiv) was added. At that stage reaction mixture was degassed using freeze-pump-thaw technique. AIBN was added (0.5 equiv) at room temperature and the degassing cycle repeated again at room temperature and liquid nitrogen. Reaction mixture was allowed to be heated at the constant temperature (80 °C) oil bath for 12 h under the atmosphere of dry $N_2$. Excess of solvent was removed in vacuo and the crude reaction mixture analyzed by $^1H$, $^{13}C$ NMR, revealed complete conversion of the starting material to the desired product. Cholestane (72%) was isolated as a white solid after recrystallization from diethyl ether/ethanol.
$^1H$ (NMR) $CDCl_3$: $\delta$ 0.4–2.0 (46H, m), $^{13}C$ (NMR) $CDCl_3$: $\delta$ 57.7, 57.3, 55.8, 48.1, 43.7, 41.2, 40.6, 39.8, 37.3, 37.2, 36.9, 36.6, 33.7, 30.2, 30.1, 29.3, 29.1, 27.9, 25.3, 24.9, 23.9, 23.6, 23.3, 21.9, 19.7, 13.3, 13.1.
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