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Organosilane-mediated Free Radical Cyclization Reactions Employing Carbonyl Traps

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Abstract: Free-radical cyclization of halocarbonyl compounds can be achieved using the organosilane reagents phenylsilane and tristrimethylsilylsilane. Both 6-exo-trig and 5-exo-trig cyclizations can be accomplished using aldehydes or ketones as radical traps. © 1998 Elsevier Science Ltd. All rights reserved.

Free-radical reactions are an important means of achieving the controlled formation of carbon-carbon bonds,¹ and are particularly useful for the construction of a wide variety of ring systems.² Most free-radical cyclizations use carbon-carbon multiple bonds as radical traps, as in the 5-*exo*-trig cyclization of 5-hexenyl radicals. In comparison, free-radical cyclizations onto carbonyl groups are less commonly encountered. Organostannane mediated cyclizations of haloaldehydes were explored by Fraser-Reid and coworkers, for the formation of cyclohexanols.³ One of the difficulties inherent in this approach is the reversibility of the radical cyclization of 1 to 2 (Scheme 1). For the parent systems, although cyclization is rapid, β -scission of the cyclized oxygen centred radical 2 is competitive, with the equilibrium favoring the ring-opened alkyl radical 1.⁴ The formation of a cyclohexanol (e.g. **4a**) via radical cyclization, and faster rate of β -scission of **2a** relative to **2b**. This problem is more severe for organostannane mediated cyclizations onto ketones, with products usually derived from trapping of carbon-centred radicals.^{5,6,3b} Although free-radical cyclizations using carbonyl traps with organostannanes have been demonstrated,⁷ the need exists for improved reagents and conditions before this strategy will become generally applicable in synthesis.



0040-4039/98/\$ - see front matter © 1998 Elsevier Science Ltd. All rights reserved. *PII*: S0040-4039(98)01585-8 Assuming the rates of radical cyclization and fragmentation are faster than the rates of H-atom transfer by M-H, then preferential formation of the cyclized product 4 over the uncyclized product 3 (Scheme 1) should occur when $k_{H-O}/k_{H-C} > k_c/k_c$.⁸ Thus, greater selectivity of the H-atom donor for trapping of oxygen-centred radicals (i.e. cyclized radical 2) versus carbon-centred radicals (i.e. uncyclized radical 1), will result in improved product ratios $4/3.^9$ Unlike tributylstannane, most organosilanes¹⁰ are relatively poor H-atom donors with carbon-centred radicals (Table 1). Triethylsilane for instance is a poor chain-transfer agent, and is rarely used for free-radical reductions. However, organosilanes are relatively good H-atom donors with oxygen-centred radicals (Table 1), and should consequently show greater selectivity for the formation of cycloalkanols 6 over direct reduction products 7 (Scheme 2).

H-atom Donor	k _{H-C} (M ⁻¹ s ⁻¹) ^b	k _{H-O} (М ⁻¹ s ⁻¹) ^с
Bu ₃ SnH	2.3 x 10 ⁶	2.2 x 10 ⁸
(Me ₃ Si) ₃ SiH	3.8 x 10 ⁵	1.1 x 10 ⁸
Et ₃ SiH	6.4 x 10 ²	5.7 x 10 ⁶
PhSiH ₃	2.9 x 10 ⁴ (at 110 ℃)	7.5 x 10 ⁶

Table 1. Rates of H-atom Abstraction of Carbon-centred and Oxygen-centred Radicals from R₃MH^a

^a Except where noted, kinetics were measured between 23 °C and 27 °C (See: Ref. 10a). ^b Radical = $RCH_{2^{\bullet}}$ ^c Radical = t-BuO•

To test our hypothesis, a number of commercially available silanes were screened with a dimethylmalonate derived bromoaldehyde for the formation of **6a**, using sealed tube conditions (Table 2).¹¹ Triethylsilane mediated reduction resulted in low yields of the cyclized product **6a**, even under neat conditions. This resulted from problems due to poor radical chain propagation, and competing ionic reduction of the aldehyde to the primary alcohol (followed by subsequent lactonization). Interestingly, use of phenylsilane¹² resulted in more promising yields of **6a**. To the best of our knowledge, this is the first example of a PhSiH₃ mediated free-radical cyclization. Use of 2 equivalents of PhSiH₃ at 80 °C with benzene or dioxane solvent, revealed that ionic reduction of the aldehyde was a major side reaction, while in MTBE or acetonitrile, only low conversion was noted. Attempts to force the reaction by employing higher temperatures, with DAB or benzoyl peroxide as initiator, resulted in a commensurate increase in the amount of direct reduction product **7**. These side reactions were minimized by using THF (or DME) at reflux, although rate constant data suggest that THF should serve as a competitive H-atom donor for oxygen-centred radicals under these conditions.¹³



Optimized conditions for cyclization employed PhSiH₃ (4 equiv.) in refluxing THF solution (0.2 M) using standard glassware or sealed ampoules (Conditions A, Table 2).¹⁴ Tributylstannane (Conditions B, Table 2) gave comparable results to those obtained with PhSiH₃ for the formation of **6a** (Entries 6 and 5, Table 2). However, in comparison to Bu₃SnH, PhSiH₃ has lower toxicity, and does not present the well known problems associated with the removal of organostannane residues from the products. Tristrimethylsilylsilane¹⁰ (Conditions C, Table 2) can also be used for these cyclizations, but phenylsilane is preferable due to its lower cost. A variety of other substrates were also tested under these conditions. As expected from the rate constant data (Scheme 1), cyclization to cyclohexanol **4a**¹⁵ (Entry 1, Table 2) occurs more readily than formation of

cyclopentanol **4b** (Entry 2, Table 2). Although the yields in this case were modest, PhSiH₃ gave better results than either Bu₃SnH or (Me₃Si)₃SiH (Entries 3 and 4, Table 2). Introduction of substituents into the chain improved the yield of the cyclized products **6a** and **6b** (Entries 5 to 9, Table 2). Interestingly, cyclopentanol **6b** formation occurred in higher yield than cyclohexanol **6a** formation, demonstrating that 5-exo-trig radical cyclizations onto aldehydes are synthetically viable. Cyclizations of aryl radicals with aldehydes, which have not been previously documented in literature, occur in only moderate yield (Entries 10 to 12, Table 2). In these cases, appreciable amounts of the uncyclized compound 7 and unreacted starting material were observed by crude NMR. Contrary to our expectations,¹⁶ the use of a catalytic thiol additive increased the yields of cyclized product **6c** using PhSiH₃ as a reductant (Entry 11, Table 2). We have also achieved direct trapping of radicals from 6 and 5-exo-trig cyclization onto ketones (Entries 13 and 14, Table 2).





^a E = COOMe. ^b Conditions: (A) PhSiH₃, in., THF, Δ ; (B) Bu₃SnH, in., PhH, Δ ; (C) (Me₃Si)₃SiH, in., PhH, Δ ; (D) PhSiH₃, RSH (30 mol%), in., THF, Δ . ^c Yields refer to chromatographically pure products except for entries 1-4, which were determined using GC.

In summary, the selectivity of organosilanes as H-atom donors for O- versus C-centred radicals allows their use in the synthesis of cyclopentanols and cyclohexanols. 6-exo-trig and 5-exo-trig free radical cyclizations of halocarbonyl compounds can be accomplished using phenylsilane and tristrimethylsilylsilane. Phenylsilane is particularly attractive, since it is less toxic than tributylstannane, and less expensive than tristrimethylsilylsilane. Further studies on free-radical cyclization reactions will be reported in due course.

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This situation will generally be the case in fast reversible cyclizations between an uncyclized carbon 9. centred radical and a cyclized oxygen-centred radical. Thus, for the oxiranyl carbinyl radical system, control of the product ratios should be possible by judicious choice of H-atom donor.

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Representative Cyclization: To a solution of bromoaldehyde (1 mmol) and DAB (0.3 mmol) in THF (5.0 14. mL) at 25 °C was rapidly added PhSiH₃ (4 mmol). The solution was refluxed for 14 h and then cooled to r.t. Water (40 mL) was added, and the mixture extracted with CH_2Cl_2 (3 x 35 mL). The combined organics were dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography (SiO₂ - EtOAc/hexanes) yielded **6a-e**.

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