

## Organosilane-mediated Free Radical Cyclization Reactions Employing Carbonyl Traps

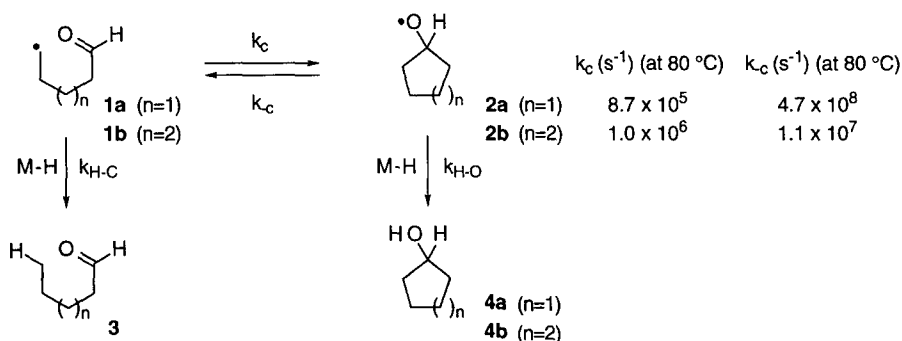
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**Abstract:** Free-radical cyclization of halocarbonyl compounds can be achieved using the organosilane reagents phenylsilane and tris(trimethylsilyl)silane. Both 6-*exo*-trig and 5-*exo*-trig cyclizations can be accomplished using aldehydes or ketones 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,<sup>1</sup> and are particularly useful for the construction of a wide variety of ring systems.<sup>2</sup> 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.<sup>3</sup> 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,  $\beta$ -scission of the cyclized oxygen centred radical **2** is competitive, with the equilibrium favoring the ring-opened alkyl radical **1**.<sup>4</sup> The formation of a cyclopentanol (e.g. **4a**) via radical cyclization is consequently less successful than formation of a cyclohexanol (e.g. **4b**), because of the slower rate of cyclization, and faster rate of  $\beta$ -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.<sup>5,6,3b</sup> Although free-radical cyclizations using carbonyl traps with organostannanes have been demonstrated,<sup>7</sup> the need exists for improved reagents and conditions before this strategy will become generally applicable in synthesis.

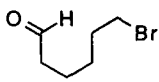
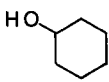
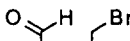



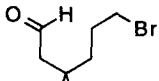
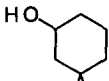

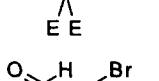
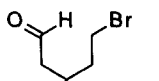

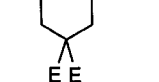
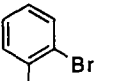
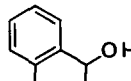
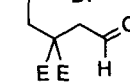
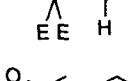
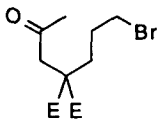
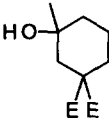
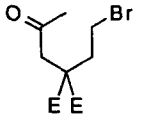
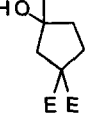


Scheme 1



cyclopentanol **4b** (Entry 2, Table 2). Although the yields in this case were modest,  $\text{PhSiH}_3$  gave better results than either  $\text{Bu}_3\text{SnH}$  or  $(\text{Me}_3\text{Si})_3\text{SiH}$  (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,<sup>16</sup> the use of a catalytic thiol additive increased the yields of cyclized product **6c** using  $\text{PhSiH}_3$  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).

**Table 2: Radical Medicated Cyclizations of Haloaldehydes and Ketones**

Entry	Substrate <sup>a</sup>	Conditions <sup>b</sup>	Product	Yield (%) <sup>c</sup>
1		A	<b>4a</b> 	52
2		A	<b>4b</b> 	29
3		B	<b>4b</b>	9
4		C	<b>4b</b>	7
5		A	<b>6a</b> 	85
6		B	<b>6a</b>	86
7		C	<b>6a</b>	71
8		A	<b>6b</b> 	93
9		B	<b>6b</b>	74
10		A	<b>6c</b> 	5
11		D	<b>6c</b>	19
12		C	<b>6c</b>	29
13		A	<b>6d</b> 	14
14		A	<b>6e</b> 	36

<sup>a</sup> E = COOMe. <sup>b</sup> Conditions: (A)  $\text{PhSiH}_3$ , in., THF,  $\Delta$ ; (B)  $\text{Bu}_3\text{SnH}$ , in., PhH,  $\Delta$ ; (C)  $(\text{Me}_3\text{Si})_3\text{SiH}$ , in., PhH,  $\Delta$ ; (D)  $\text{PhSiH}_3$ , RSH (30 mol%), in., THF,  $\Delta$ . <sup>c</sup> 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 cyclopentanol and cyclohexanol. 6-*exo*-trig and 5-*exo*-trig free radical cyclizations of halocarbonyl compounds can be accomplished using phenylsilane and tris(trimethylsilyl)silane. Phenylsilane is particularly attractive, since it is less toxic than tributylstannane, and less expensive than tris(trimethylsilyl)silane. Further studies on free-radical cyclization reactions will be reported in due course.

**Acknowledgment.** This work was supported by the Natural Science and Engineering Research Council of Canada. D.B.M. thanks the University of Toronto for a scholarship.

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- For Scheme 1, when [M-H] remains constant through the course of the reaction (e.g. for a large excess of M-H), H-atom trapping will be pseudo-first-order, and the kinetics simplify to those of a Curtin-Hammett / Winstein-Holness system with "Feed-In" mechanism. Under these conditions, the final product ratio is approximated by the equation:  $[4]/[3] = (k_c k_{H-O} / k_{H-C}) / \{k_c + (k_{H-O}[M-H])\}$ . See: (a) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83-134. (b) Seeman, J. I.; Sanders, E. B.; Farone, W. A. *Tetrahedron* **1980**, *36*, 1173-1177.
- This situation will generally be the case in fast reversible cyclizations between an uncyclized carbon 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.
- A number of organosilanes are useful radical reductants, see: (a) Chatgililoglu, C. *Chem. Rev.* **1995**, *95*, 1229-1251. (b) Chatgililoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188-194, and references cited therein.
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- Representative Cyclization: To a solution of bromoaldehyde (1 mmol) and DAB (0.3 mmol) in THF (5.0 mL) at 25 °C was rapidly added PhSiH<sub>3</sub> (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<sub>2</sub>Cl<sub>2</sub> (3 x 35 mL). The combined organics were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Flash chromatography (SiO<sub>2</sub> - EtOAc/hexanes) yielded **6a-e**.
- Bu<sub>3</sub>SnH gives only trace amounts of cyclohexanol under free-radical conditions, see: Flies, F.; Lalande, R.; Maillard, B. *Tetrahedron Lett.* **1976**, *17*, 439-442.
- We expected to observe an increase in the amount of the uncyclized product **7** using *t*-dodecanethiol as a polarity reversal catalyst, see: Cole, S. J.; Kirwan, J. N.; Roberts, B. P.; Willis, C. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 103-112.