Intramolecular Free Radical Cyclizations Using Acylsilanes as Radicalphiles

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**Abstract**  Carbon radicals add intramolecularly to acylsilanes at the carbonyl carbon followed by radical Brook rearrangement to give silylated cyclopentanols or cyclohexanols in good yields.

The use of radical reactions in organic syntheses has been studied very intensively in recent years; however, the attentions are mostly centered on radical additions to carbon-carbon multiple bonds. Although there are some recent novel applications about addition of carbon radicals to carbonyls, the research in this direction is quite scarce. Kinetic studies revealed that radical additions to carbonyls are reversible and the fragmentation rates are faster than the cyclization rates (Scheme 1). Thus it is not surprising that cyclizations of this type are most successful in some quite rigid systems where Thorpe-Ingold effect operates. Others elegantly manipulated this reversible phenomenon in ring enlargement processes.

**Scheme 1**

\[
\begin{align*}
\text{carbon radical} & \text{acylsilane} \\
\text{cyclization} & \text{fragmentation}
\end{align*}
\]

We are also interested in radical additions to carbonyls. Conceptually, if one wishes to shift the equilibrium towards the cyclization side one should design a system in which the stability of the alkoxy radical is enhanced or trap the alkoxy radical irreversibly as soon as it is formed. Acylsilane appears to be an excellent candidate along this line because silyl group is known to be able to stabilize radical or pol of it (Scheme 2). The possibility of an irreversible radical Brook rearrangement is also likely. In this communication we wish to report our initial success in this direction.

We first prepared bromide 2a (79%) by alkylatlon of silyldihiane with 1,4-dibromobutane (Scheme 3). Hydrolysis of 2a gave the desired bromoacylsilane 3a in 86% yield. Compounds such as 2a are not stable and we recommend to perform the hydrolysis step using the crude product as soon as it is obtained.

Slow addition of a solution of tributyltin hydride and catalytic amount of
azobisisobutyronitrile (AIBN) in benzene to a solution of 3a in benzene (0.1 M) heated at 80°C gave cyclopentyl trimethylsilyl ether (4a) as the only product by GC analysis and no straight reduction product was detected. However, since 4a was too volatile to be completely removed from benzene, we directly treated the cyclization mixture with a tetrahydrofuran solution of tetrabutylammonium fluoride, benzoyl chloride and trimethylamine to give the benzoate 13a in 68% isolation yield. Similarly, bromoacylsilane 3b (64% from 1) also gave benzoate 13b (62%) under the same reaction conditions. Thus, it is most likely that the radical cyclization process occurred in an exo mode followed by a Brook rearrangement as expected (Scheme 2). We were not able to detect any product derived from endo mode of cyclization.

It is well-known that in radical cyclization reactions steric hindrance at the site of attack decreases the cyclization rate. Therefore, it is interesting to examine the effect of the steric bulkiness of the silyl group on the acylsilane cyclization reactions. Bromoacylsilane 7a (54%) was synthesized from 5 accordingly. Under the same cyclization conditions, we were able to isolate the less volatile silyl ether 8a in 80% yield. Again no other types of product were found. Even in the case of the cyclization of 11a (73% from 9), silyl ether 12a was the only product isolated (81%). Apparently the steric effect of the silyl group is minimal at least for the silyl groups that we choose.

Since chloroacylsilane such as 14 can be prepared in higher yield via alkylation of 9 with 1-bromo-4-chlorobutane (92%) followed by hydrolysis (91%), we decided to see if this kind of chloro compound could be useful. As shown in equation (1), under the same reaction conditions mentioned above we were able to isolate in 47% yield of the expected cyclization product 12a in addition to 3% of straight reduction product 15, 13% of 16, 30% of 17, and 6% of 18. α-Silyl alcohol 16 is probably derived from tin hydride reduction of the alcohol.
Table 1. Concentration study of the cyclization of acylsilane 11a.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Concentration (M)b</th>
<th>Time (h)c</th>
<th>Ratio (cyclization/reduction)d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td>6</td>
<td>100/0</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>2</td>
<td>100/0</td>
</tr>
<tr>
<td>3e</td>
<td>0.5</td>
<td>1</td>
<td>100/0</td>
</tr>
<tr>
<td>4f</td>
<td>0.2</td>
<td>0.5</td>
<td>90/10</td>
</tr>
</tbody>
</table>

aThe reaction was performed by slow addition of a solution of tributyltin hydride (1.3 equiv) and AIBN (5 mol%) in benzene to a solution of 11a in benzene heated at 80°C under nitrogen. bThe concentration is the final concentration based on 11a. The initial concentration of 11a is double of this number. cThe time is the addition time of tributyltin hydride solution. dThe ratios were determined by 1H NMR integration of the crude product. eAn 80% isolation yield of the cyclization product 12a was obtained. fPerformed by direct mixing of 11a, tributyltin hydride (1.3 equiv) and AIBN (5 mol%) in benzene and heated under nitrogen at 80°C for 0.5 h.

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Bu₃SnH (2 equiv, slow addition, 6 h) + AIBN (cat), PhH 80°C

12a + 15 (eq 1)

Σ = Ph₂MeSi

16 X = Cl 13%
17 X = H 30%
18 6%

Further reduction of 16 gives 17. The exact origin of silyl ether 18 is not certain at this point and requires more detailed investigations. Thus it is revealed in this experiment that the rate of reduction of the acylsilane moiety by tributyltin hydride was comparable with that of the chlorides. This certainly imposes some limitations for this kind of cyclizations.

In order to see how efficient this type of cyclization is, we conducted a concentration study. As shown in Table 1, even direct heating of 11a and tributyltin hydride in benzene gave mostly the cyclization product (entry 4). In fact the cyclization reaction can be performed very practically by slow addition of tributyltin hydride over a relatively short period of time with a rather concentrated solution (entry 3).

In summary, the previously unnoticed radical chemistry of acylsilanes has been examined. Our experiments indicate that acylsilanes are excellent radical acceptors. This methodology constitutes a novel entry for the synthesis of molecules with cyclopentanol or cyclohexanol skeleton under neutral condition.

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References and Notes


10. All new compounds mentioned gave satisfactory 1H NMR, 13C NMR, IR and elementary analysis.


12. Controlled experiment indicated that 3a was stable by heating in benzene under reflux overnight.

13. Although to our knowledge the reduction of acylsilane with tributyltin hydride has not been reported, the reduction of carbonyl with tin hydride is well-known, see: Pereyre, Y.; Quintard, J.-P.; Rahm, A. Tin in Organic Synthesis; Butterworth: Boston, 1987; Chapter 4, pp. 69-80. For more recent example, see: Enholm, E. J.; Prasad, G. Tetrahedron Lett. 1989, 30, 4939.

14. Simply heating 17 in benzene at reflux temperature overnight did not give 18.

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