Tetrahedron Letters, Vol.32, No 29, pp 3515-3518, 1991
Printed in Great Britain

0040-4039/91 $3.00 + 0
Pergamon Press plc

Intramolecular Free Radical Cyclizations Using Acylsilanes as Radicalphiles

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Key Words radical cyclization, acylsilane, radical Brook rearrangement, radical addition to carbonyl; cyclopentanol

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 synthesis has been studied very intensively in recent years;[1] 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,[2] 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).[3] Thus it is not surprising that cyclizations of this type are most successful in some quite rigid systems[2a, 2c] where Thorpe-Ingold effect[4] operates. Others elegantly manipulated this reversible phenomenon in ring enlargement processes.[2d-g]

Scheme 1

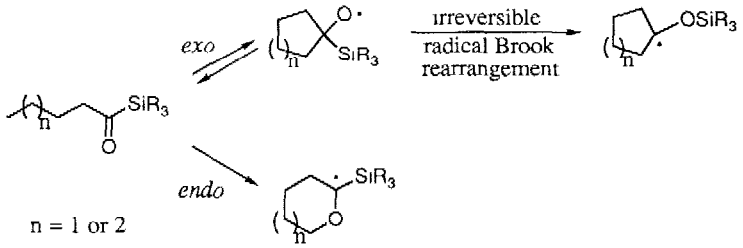
$k_1 = 8.7 \times 10^5\ s^{-1}$ (80°C) $\quad k_2 = 1.0 \times 10^6\ s^{-1}$ (80°C)
$k_{-1} = 4.7 \times 10^8\ s^{-1}$ (80°C) $\quad k_{-2} = 1.1 \times 10^7\ s^{-1}$ (80°C)

We are also interested in radical additions to carbonyls. Conceptually, if one wishes to shift the equilibrium towards the cyclization side one should design either 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[5] appears to be excellent candidate along this line because silyl group is known to be able to stabilize radical α[6a-c, 7] or β[6] to it (Scheme 2). The possibility of an irreversible radical Brook rearrangement[8] is also likely. In this communication we wish to report our initial success in this direction.

We first prepared bromide **2a** (79%) by alkylation of silyldithiane **1**[9] with 1,4-dibromobutane (Scheme 3).[10] Hydrolysis [11] of **2a** gave the desired bromoacylsilane **3a** in 86% yield.[12] 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 (6 h) of a solution of tributyltin hydride (1.3 equiv, 0.13 M) and catalytic amount of

Scheme 2

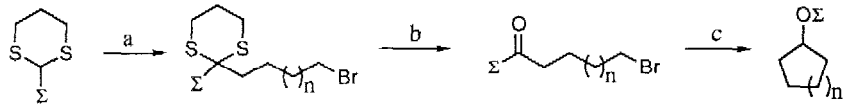


azobisisobutyronitrile (AIBN) in benzene to a solution of **3a** in benzene (0.1 M) heated at 80°C gave cyclopentyl trimethylsilyl ether (**4a**) as the only product by GC analysis and no straight reduction product was detected. However, since **4a** was too volatile to be completely removed from benzene we directly treated the cyclization mixture with a tetrahydrofuran solution of tetrabutylammonium fluoride, benzoyl chloride and triethylamine 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 [1a] 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 condition 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

Scheme 3



a n = 1 **b** n = 2

1 Σ = Me_3Si **2** Σ = Me_3Si **3** Σ = Me_3Si **4** Σ = Me_3Si

5 Σ = $^tBuMe_2Si$ **6** Σ = $^tBuMe_2Si$ **7** Σ = $^tBuMe_2Si$ **8** Σ = $^tBuMe_2Si$

9 Σ = Ph_2MeSi **10** Σ = Ph_2MeSi **11** Σ = Ph_2MeSi **12** Σ = Ph_2MeSi

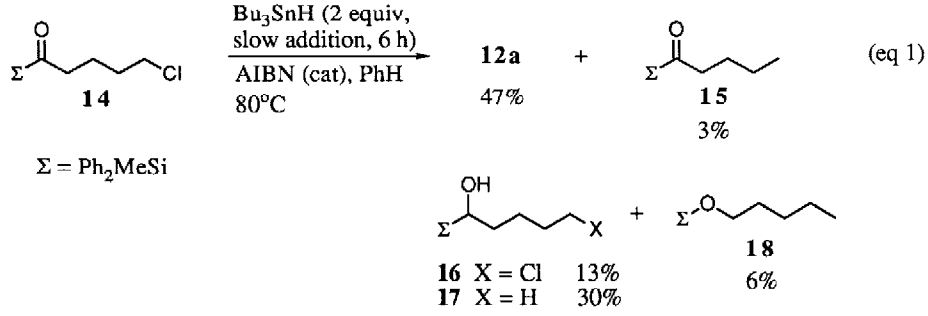
13 Σ = COPh

(a) BuLi (1 equiv), THF; $BrCH_2CH_2(CH_2)_nCH_2Br$ (2 equiv) (b) HgO (2 equiv), BF_3·OEt (2 equiv), Celite, THF, H_2O (c) Bu_3SnH (1.3 equiv), AIBN (5 mol%), PhH, 80°C (d) Bu_4NF (2.5 equiv)/THF, PhCOCl (5 equiv), Et_3N (4 equiv), 80°C

Table 1. Concentration study of the cyclization of acylsilane **11a**.[a]

Entry	Concentration (M)[b]	Time (h)[c]	Ratio (cyclization/reduction)[d]
1	0.05	6	100/0
2	0.2	2	100/0
3[e]	0.5	1	100/0
4[f]	0.2	0.5	90/10

[a]The 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. [b]The concentration is the final concentration based on **11a**. The initial concentration of **11a** is double of this number. [c]The time is the addition time of tributyltin hydride solution. [d]The ratios were determined by ^{1}H NMR integration of the crude product [e]An 80% isolation yield of the cyclization product **12a** was obtained. [f]Performed 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.



carbonyl.[13] Further reduction of **16** gives **17**. The exact origin of silyl ether **18** is not certain at this point and requires more detailed investigations.[14] 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[5] 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.

Acknowledgements. Financial support by the National Science Council of the Republic of China is gratefully acknowledged.

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

(Received in Japan 27 February 1991)