Tetrahedron Letters 75 (2021) 153144

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

In-situ-generation of alkylsilyl peroxides from alkyl hydroperoxides and their subsequent copper-catalyzed functionalization with organosilicon compounds

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ARTICLE INFO

Article history:
Received 27 February 2021
Revised 15 April 2021
Accepted 28 April 2021
Available online 30 May 2021

Keywords:
Copper(I) iodide
Alkylsilyl peroxides
Organosilicon compounds
Radical-based approaches
Cyanation

ABSTRACT

Alkylsilyl peroxides were generated *in situ* from the corresponding alkyl hydroperoxides using organosilicon compounds of the type Me_3SiX (X = CN, N_3, and halogens) and an amine base. Subsequent *in situ* copper-catalyzed homolytic cleavage of the alkylsilyl peroxides afforded alkyl radicals, which were then trapped with X (X = CN, N_3, and halogens) to furnish products with new carbon-carbon, carbon-nitrogen, or carbon-halogen bonds in good to high yields.

Introduction

Chemical reactions that involve alkyl radicals are often powerful synthetic tools in organic chemistry [1,2]. The development of synthetic methods for the generation of alkyl radicals [3] has gained considerable attention, as the unique properties of reactive open-shell species enable bond disconnections that are unattainable *via* the use of ionic species [1]. Over several years, we have developed a Cu-catalyzed method to generate alkyl radicals from alkylsilyl peroxides (ASPs) **1** [4] under mild reductive conditions (a reductive β-scission strategy), and we have applied this method to organic synthesis. ASPs **1** are easily handled and can be readily synthesized from a variety of alkyl radical precursors using Cu [5], Fe [6] and Ni [7] catalysis. As part of our continuous studies on radical-promoted transformations using ASPs **1**, we have recently reported the Cu-catalyzed cyanation and azidation of cyclic ASP **1a** with trimethylsilyl cyanide (Me_3SiCN) and trimethylsilyl azide (Me_3SiN_3), respectively (Scheme 1a) [8]. Based on these results, we hypothesized that under similar reaction conditions, it might be possible to generate ASPs **1** *in situ* from the corresponding alkyl hydroperoxide **3** and a specific Me_3SiX reagent (e.g. X = CN or N_3) (Scheme 1b). Herein, we report the realization of this new approach, starting from alkyl hydroperoxide **3**, that utilizes cyanation, azidation, or halogenation reactions.

Results and discussion

The attempted reaction of **3a** with Me_3SiCN (2 equiv.) in the presence of 5 mol% each of CuI and the amine ligand 1,10-phenanthroline (1,10-Phen) was carried out in dimethylformamide (DMF) at room temperature for 0.5 h to furnish 5-cyano-1-phenylpent-1-one (**2a**) in 88% yield (Table 1, entry 1). A two-mmol-scale reaction of **3a** afforded **2a** in 80% yield (Entry 1; 76% isolated yield). Decreasing the quantity of Me_3SiCN marginally decreased the yield of **2a** (Entry 2). Increasing the temperature to 60 °C slightly improved the yield (Entry 3). Switching the solvent from DMF to MeCN under otherwise similar conditions afforded **2a** in 89% yield (Entry 4). Use of the 2,2′-bipyridyl ligand instead of 1,10-Phen lowered the yield of **2a** (Entry 5). The effect imparted by the amine additive was found to be critical. Use of 4-dimethylamino-pyridine (DMAP) as the amine additive decreased the yield of **2a** (Entry 6). Reducing the number of equivalents of DMAP used also reduced the yield (Entry 7 vs. entry 6). The use of triethylamine, *N*,*N*-diisopropylethylamine (DIPEA), and 1,4-diazabicycle[2.2.2]-octane (DABCO) gave unsatisfactory results (Entries 8–12). It should also be noted that the reaction does not proceed in the absence of the CuI catalyst. With the optimum conditions for the cyanation

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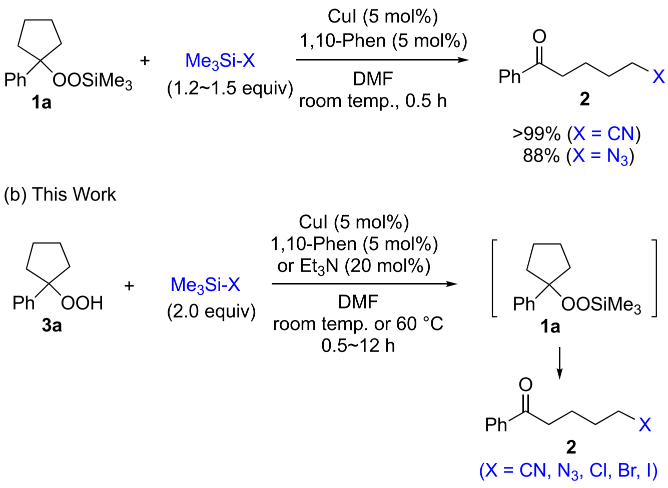
https://doi.org/10.1016/j.tetlet.2021.153144



Scheme 1. Radical-based approaches for the synthesis of functionallized **2**.

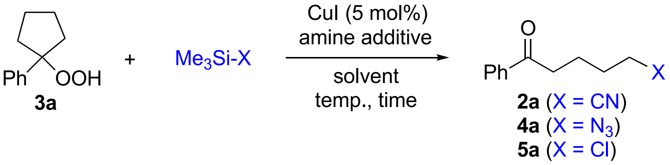
reaction in hand (Entry 3), the azidation reaction of **3a** with Me$_3$SiN$_3$ (2 equiv.) in DMF was carried out in the presence of 5 mol% of both CuI and 1,10-Phen varying the temperature and the reaction time to furnish 5-azido-1-phenylpent-1-one (**4a**) in high yield (Entries 14 and 15 vs. entry 13). Several different amine bases were used with different reaction times and temperatures (Entries 15–19). The use of a catalytic amount of triethylamine provided **4a** in a similarly high yield (Entry 18). Interestingly, this transformation is also applicable to the halogenation of **3a**. For example, the chlorination of **3a** with Me$_3$SiCl (2 equiv.) was undertaken with a catalytic quantity of CuI and 1,10-Phen (5 mol% each) in DMF at room temperature, giving coupling product **5a** in high yield (Entry 20). The screening of amine bases revealed that a catalytic amount of triethylamine is also preferrable for the smooth coupling of **3a** with Me$_3$SiCl (Entry 23 vs. entries 21, 25, and 26). Importantly, the use of 1.2 equiv. of Me$_3$SiCl afforded the chlorination product **5a** in an almost quantitative yield (Entry 24).

With the optimized conditions in hand for several different transformations, we subsequently examined the scope of the CuI-catalyzed radical functionalization of several cyclic alkyl hydroperoxides **3a-f** as shown in Table 2. Thus, cyanation of five different alkyl hydroperoxides **3a-f** with Me$_3$SiCN gave the corresponding cyanation products **2a-f**, respectively, in good to high yields (Entries 1, 6, 11, 16, 21, and 26). In a similar manner, azidation of **3a-f** afforded azidation products **4a-f**, respectively, in good to high yields (Entries 2, 7, 12, 17, 22, and 27). With respect to the halogenation reactions, not only was the chlorination of alkyl hydroperoxides **3a-f** realized, but the bromination and iodination of these substrates were also achieved to give the corresponding halogenation products **5a-f**, **6a-f** and **7a-f**, respectively in good to excellent yield (Entries 3–5, 8–10, 13–15, 18–20, 23–25, and 28–30). Alkyl hydroperoxide **3 g** was successfully transformed to the corresponding functionalized methyl ketones **2 g**, **4 g**, and **5 g** in low to good yields (Entries 31–33).

Shown in Scheme 2 is our proposed catalytic cycle for the *in-situ*-generation of alkylsilyl peroxides from the corresponding alkyl hydroperoxides, and the subsequent copper-catalyzed homolytic cleavage of the alkylsilyl peroxides using an organosilicon

Table 1

Optimization of the reaction conditions for the radical functionalization of alkyl hydroperoxides **3a**.[a]

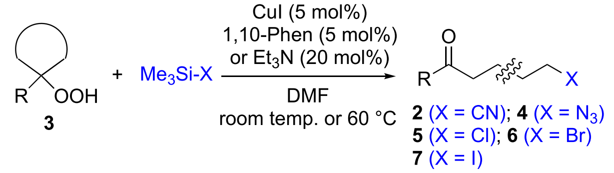


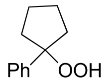
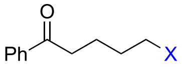
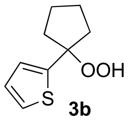
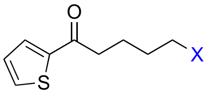
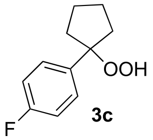
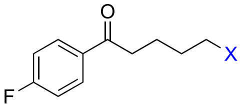
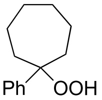
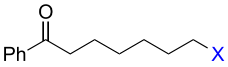
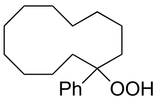
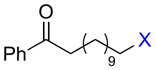
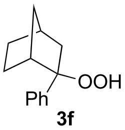
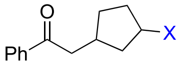
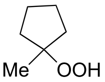
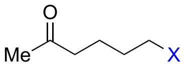
Entry	Me$_3$SiX (equiv.)	Amine (equiv.)	Solvent	Temp (°C), Time (h)	Yield (%)[b]
1	Me$_3$SiCN (2)	1,10-Phen (0.05)	DMF	RT, 0.5	88(80)[c]
2	Me$_3$SiCN (1.2)	1,10-Phen (0.05)	DMF	RT, 0.5	71
3	Me$_3$SiCN (2)	1,10-Phen (0.05)	DMF	60, 0.5	90
4	Me$_3$SiCN (2)	1,10-Phen (0.05)	MeCN	RT, 0.5	89
5	Me$_3$SiCN (2)	2,2-Bipyridyl (0.05)	DMF	RT, 0.5	62
6	Me$_3$SiCN (2)	DMAP (1)	DMF	RT, 6	50
7	Me$_3$SiCN (2)	DMAP (0.2)	DMF	RT, 12	25
8	Me$_3$SiCN (2)	Et$_3$N (1)	DMF	RT, 6	22
9	Me$_3$SiCN (2)	Et$_3$N (0.2)	DMF	RT, 12	39
10	Me$_3$SiCN (2)	Et$_3$N (0.2)	DMF	60, 12	26
11	Me$_3$SiCN (2)	DIPEA (1)	DMF	RT, 6	53
12	Me$_3$SiCN (2)	DABCO (1)	DMF	RT, 6	<5
13	Me$_3$SiN$_3$ (2)	1,10-Phen (0.05)	DMF	RT, 0.5	28
14	Me$_3$SiN$_3$ (2)	1,10-Phen (0.05)	DMF	RT, 12	26
15	Me$_3$SiN$_3$ (2)	1,10-Phen (0.05)	DMF	60, 12	81
16	Me$_3$SiN$_3$ (2)	DMAP (1)	DMF	RT, 6	5
17	Me$_3$SiN$_3$ (2)	Et$_3$N (0.2)	DMF	RT, 12	19
18	Me$_3$SiN$_3$ (2)	Et$_3$N (0.2)	DMF	60, 12	78
19	Me$_3$SiN$_3$ (2)	DIPEA (1)	DMF	RT, 6	13
20	Me$_3$SiCl (2)	1,10-Phen (0.05)	DMF	RT, 12	85
21	Me$_3$SiCl (2)	DMAP (1)	DMF	RT, 12	86
22	Me$_3$SiCl (2)	Et$_3$N (1)	DMF	RT, 12	90
23	Me$_3$SiCl (2)	Et$_3$N (0.2)	DMF	RT, 12	99
24	Me$_3$SiCl (1.2)	Et$_3$N (0.2)	DMF	RT, 12	99
25	Me$_3$SiCl (2)	DIPEA (1)	DMF	RT, 12	87
26	Me$_3$SiCl (2)	DABCO (1)	DMF	RT, 12	91

[a] Unless otherwise noted, the reactions of **3a** (0.2 mmol) and Me$_3$SiX (2 equiv.) were carried out in the presence of copper(I) iodide (5 mol%) and an amine additive in the specified solvent (1 mL) under the indicated reaction conditions.

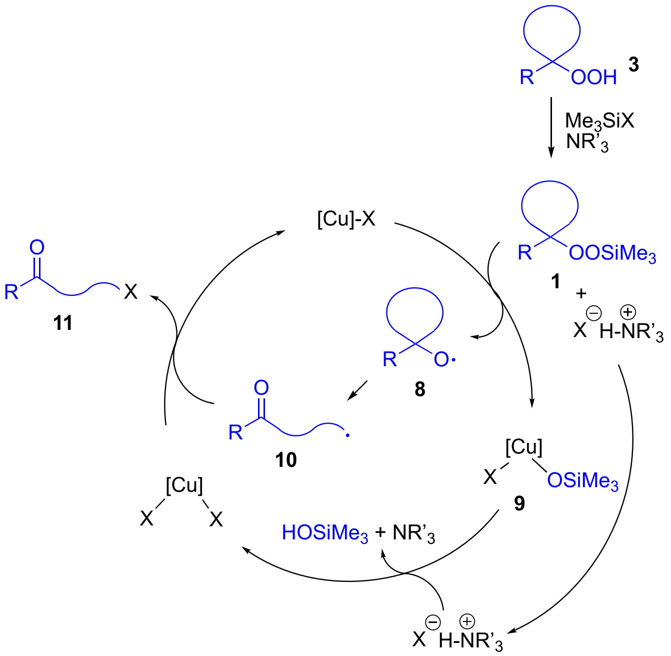
[b] Determined using ^{1}H NMR spectroscopy with CH$_3$NO$_2$ as an internal standard. [c]Two-mmol-scale experiment of **3a** at RT for 0.5 h.

Table 2
Scope for the functionalization of alkyl hydroperoxides[a]



Entry	Alkyl Hydroperoxides	Products[b,c]
1 2 3 4 5	 **3a**	 **2a** (X = CN), 88% (85%) **4a** (X = N_3), 81% (79%) **5a** (X = Cl), 99% (93%) **6a** (X = Br), 97% (87%) **7a** (X = I),[d] 92% (86%)
6 7 8 9 10	 **3b**	 **2b** (X = CN), 64% (57%) **4b** (X = N_3), 84% (78%) **5b** (X = Cl), 89% (81%) **6b** (X = Br), 92% (89%) **7b** (X = I),[d] 91% (81%)
11 12 13 14 15	 **3c**	 **2c** (X = CN), 78% (75%) **4c** (X = N_3), 57% (43%) **5c** (X = Cl), 96% (85%) **6c** (X = Br), 93% (95%) **7c** (X = I),[d] 72% (74%)
16 17 18 19 20	 **3d**	 **2d** (X = CN), 82% (77%) **4d** (X = N_3), 61% (53%) **5d** (X = Cl), 75% (69%) **6d** (X = Br), 75% (69%) **7d** (X = I),[d] 58% (51%)
21 22 23 24 25	 **3e**	 **2e** (X = CN), 74% (64%) **4e** (X = N_3), 63% (63%)[e] **5e** (X = Cl), 77% (74%) **6e** (X = Br), 65% (64%) **7e** (X = I),[d] 52% (52%)
26 27 28 29 30	 **3f**	 **2f** (X = CN), 92% (85%) (dr = 1:1) **4f** (X = N_3), 70% (63%) (dr = 1:1) **5f** (X = Cl), 72% (61%) (dr = 1:1) **6f** (X = Br), 98% (93%) (dr = 1:1) **7f** (X = I),[d] 99% (85%) (dr = 1:1)
31 32 33	 **3g**	 **2g** (X = CN),[f] 27% (24%) **4g** (X = N_3), 60% (58%) **5g** (X = Cl), 70% (67%)

[a] Unless otherwise specified, the reactions were carried out as follows: [A] cyanation of **3** (0.2 mmol) using Me_3SiCN (2 equiv.) was performed in the presence of CuI and 1,10-Phen (5 mol% each) in DMF (1 mL) at room temperature for 0.5 h; [B] azidation of **3** (0.2 mmol) using Me_3SiN_3 (2 equiv.) was performed in the presence of CuI and 1,10-Phen (5 mol% each) in DMF (1 mL) at 60 °C for 12 h; [C] halogenation of **3** (0.2 mmol) using Me_3SiX (X = Cl, Br, I) (1.2 equiv.) was performed in the presence of CuI (5 mol%) and Et_3N (20 mol%) in DMF (1 mL) at room temperature for 12 h. [b] Yield determined using ^1H NMR spectroscopy with CH_3NO_2 as an internal standard. [c] Yield in parenthesis refers to the isolated yield. [d] For 1 h. [e] Me_3SiN_3 (3 equiv.). [f] Use of 1,10-Phen (10 mol%) at 60 °C.



Scheme 2. Proposed reaction mechanism.

compound of the type Me_3SiX (X = CN, N_3, and halogen) and an amine base. In the presence of Me_3SiX and the amine base (NR_3), alkyl hydroperoxide **3** transforms into the corresponding alkylsilyl peroxide **1**. The resulting alkylsilyl peroxide **1** decomposes in the presence of a nitrogen-coordinated copper species, which leads to the generation of alkoxy radical **8** and copper silanoxide complex **9**. Subsequent β-fragmentation of **8** would generate the corresponding alkyl radical **10**. After a ligand exchange on the copper center between an ammonium salt (R_3NHX) and a silanoxide, the coupling of the alkyl radical and the copper-X complex finally affords the desired product **11**.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work is dedicated to Professor Stephen F. Martin for his long-time journal editorship and significant contributions to organic chemistry. This work was financially supported by the National Natural Science Foundation of China (No. 21977019, 22050410279), and the Guangdong Provincial Key Research and Development Program (2019B020201005).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153144.

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