

Microwave-Assisted Tertiary Carbon Radical Reaction for Construction of Quaternary Carbon Center

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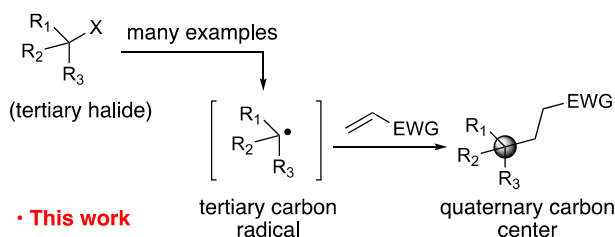
1 Microwave-assisted tertiary carbon radical reaction
2 was developed. The reaction of tertiary xanthates with
3 electron deficient alkenes was prompted by microwave
4 irradiation, and various coupling products possessing
5 quaternary carbon centers were obtained in good yields. The
6 reaction was conducted under simple and common radical
7 condition except for microwave irradiation, and the reaction
8 completes within 5 min.

9 **Keywords:** Tertiary carbon radical, Quaternary carbon
10 center, Xanthate

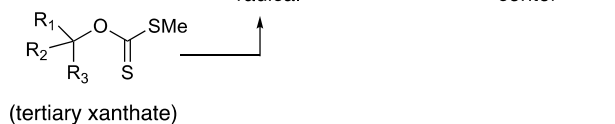
11 Construction of quaternary carbon center is an
12 important topic in synthetic organic chemistry, and the
13 intermolecular reaction of tertiary carbon radicals with
14 electron deficient alkenes is considered to be one of the
15 most powerful and direct method for it.^{1,2} Tertiary carbon
16 radicals were generated from tertiary halides in many cases,
17 and the reactions of various halides mainly including
18 bridgehead halides with alkenes have been reported.^{3,4}
19 However, the difficult preparation method and instability
20 are the typical drawbacks of tertiary halides to be applied in
21 the synthesis of complex molecules. On the other hand,
22 tertiary alcohols are commercially available, readily
23 prepared and manipulated compared to tertiary halides.
24 Nonetheless, there have been only a few examples which
25 apply tertiary alcohols for intermolecular C-C bond forming
26 reactions through tertiary carbon radical.⁵ Recently,
27 Overman *et al.* reported the photoredox-catalyzed
28 intermolecular conjugate addition reaction of electron
29 deficient alkenes with the tertiary carbon radical generated
30 from *N*-phthalimidoyl oxalate.⁶ Overman and MacMillan
31 also reported another photoredox-catalyzed reaction with
32 tertiary oxalates.⁷ These photoredox-catalyzed reactions using
33 oxalates recently have attracted much attention as an
34 alternative source of tertiary carbon radicals.⁸ So, in our
35 study of total synthesis, where we need to construct a
36 quaternary carbon center from the bridgehead tertiary
37 alcohol, we tried to apply the photoredox-catalyzed radical
38 conjugate addition through oxalates. However, in the case of
39 our substrate, tertiary alcohol could not be led to oxalate due
40 to the strong electron withdrawing property of the
41 corresponding oxalate, which resulted in an undesired
42 rearrangement product via a carbocation generated by the
43 elimination of oxalate. Thus, we require a similar radical
44 addition reaction induced from a xanthate as a weak electron
45 withdrawing group. However, to the best of our knowledge,
46 only one example of the reaction of 1-adamantanyl xanthate
47 with vinylsulfone has so far been reported by Togo *et al.* as
48 the intermolecular C-C bond forming reaction of tertiary
49 xanthates with electron deficient alkenes,^{5e} whereas the

50 reaction with allyltributyltin is slightly introduced.⁹ Herein,
51 we report a common and fast intermolecular C-C bond
52 forming reaction of tertiary xanthates with various electron
53 deficient alkenes under microwave condition.

• Conventional method



• This work



55 (tertiary xanthate)

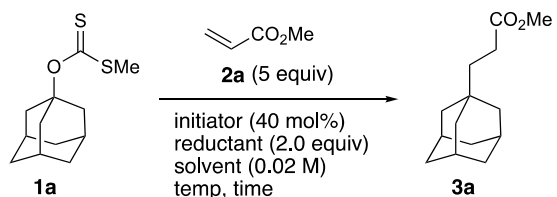
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57 **Scheme 1.** Construction of quaternary carbon center via tertiary carbon
58 radical.

59 We first examined the reaction of 1-adamantanyl
60 xanthate **1a** with methyl acrylate **2a** as a model reaction in
61 our study of total synthesis (Table 1). Although the slow
62 addition of reductant using syringe pump is generally
63 effective for radical mediated C-C bond forming reactions,
64 we tried to develop a concise reaction without the use of
65 syringe pump considering a very small scale reaction at late
66 stage of total synthesis. First, the reaction of **1a** with **2a** was
67 conducted by using V-40 and ⁿBu₃SnH in toluene at 110 °C.
68 The desired C-C bond forming reaction proceeded to give
69 only 27% of **3a** (entry 1). Higher reaction temperature at
70 140 °C slightly increased the yield to 32% (entry 2).
71 Surprisingly, the similar reaction condition with microwave
72 (MW) irradiation¹⁰ for 10 min greatly improved the yield to
73 84% (entry 3). Thus, we found that the microwave
74 irradiation is effective for tertiary carbon radical reaction
75 from xanthates. Next, we investigated the reaction
76 temperature with MW irradiation. Although lower
77 temperature (110 °C) substantially decreased the yield
78 despite MW irradiation (entry 4), the similar reaction at
79 higher temperature (180 °C) afforded **3a** in 92% yield (entry
80 5). The reactions using other radical initiators such as V-70
81 and AIBN also proceeded smoothly, with 96% and 99%
82 yield of **3a**, respectively (entries 6 and 7). The use of other
83 reducing agents such as silane also gave **3a** in 99% yield
84 (entry 8). When the amount of **2a** was reduced to 2.5 equiv,
85 the yield of **3a** was slightly decreased (entry 9). Finally, the

1 reaction was virtually completed within 5 min affording **3a**
2 in 99% yield (entry 10).

3 **Table 1.** Tertiary carbon radical mediated C-C bond forming reaction
4 of 1-adamantanyl xanthate **1a** with methyl acrylate **2a**.



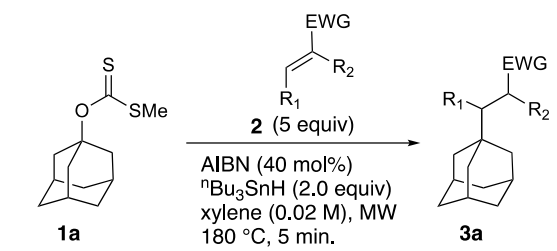
entry	initiator	reductant	solvent	temp. (°C)	time (min)	yield ^a (%)
1	V-40	ⁿ Bu ₃ SnH	PhMe ^b	110	120	27
2	V-40	ⁿ Bu ₃ SnH	xylene ^b	140	140	32
3	V-40	ⁿ Bu ₃ SnH	xylene	140 (MW) ^d	10	84
4	V-40	ⁿ Bu ₃ SnH	xylene	110 (MW) ^d	10	38
5	V-40	ⁿ Bu ₃ SnH	xylene	180 (MW) ^d	10	92
6	V-70	ⁿ Bu ₃ SnH	xylene	180 (MW) ^d	10	96
7	AIBN	ⁿ Bu ₃ SnH	xylene	180 (MW) ^d	10	99
8	AIBN	(TMS) ₃ SiH	xylene	180 (MW) ^d	10	99
9 ^c	AIBN	ⁿ Bu ₃ SnH	xylene	180 (MW) ^d	10	82
10	AIBN	ⁿ Bu ₃ SnH	xylene	180 (MW) ^d	5	99

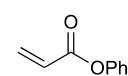
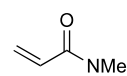

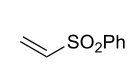
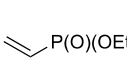

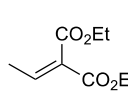
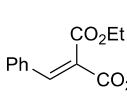

5
6 ^aNMR yield using CHBr₃ as an internal standard. ^bThe reaction was
7 conducted in 0.075 M solution. ^c2.5 equiv of **2a** was used. ^d300W of
8 microwave was irradiated under 300 psi.

9 Having established the efficient condition, we next
10 investigated various alkenes as the radical acceptor (Table
11 2).¹¹ The reactions with phenyl ester **2b** as another
12 unsaturated ester also proceeded smoothly to give C-C bond
13 forming product in 96% yield. Alkenes having electron-
14 withdrawing groups such as amide (**2c**), nitrile (**2d**), and
15 sulfone (**2e**) also reacted with **1a** giving high yields of the
16 products 99%, 99%, and 85%, respectively. On the other
17 hand, phosphonate **2f** showed a decline in yield, giving 64%
18 of the coupling product. Next, α,β -unsaturated esters
19 possessing α -substituent were examined. Methyl substituent
20 of acrylonitrile did not disturb the reaction, and **2g** afforded
21 desired coupling product in high yield. We found that even
22 β -substituents such as methyl and phenyl groups did not
23 disturb the reaction, and the reactions with **2h** and **2i**
24 proceeded in 71% and 67%, respectively. Moreover,
25 cyclopenten-1-one **2j** as a ketone analog also reacted,
26 although the yield was low. In addition, other alkenes

27 possessing free carboxylic acid also gave the desired
28 coupling product in acceptable NMR yields, though
29 purification was difficult due to its high polarity.¹² Thus, our
30 microwave-assisted carbon radical reaction was proved to
31 be applicable to various electron deficient alkenes.

32 **Table 2.** The reaction of 1-adamantanyl xanthate **1a** with various
33 electron deficient alkenes.

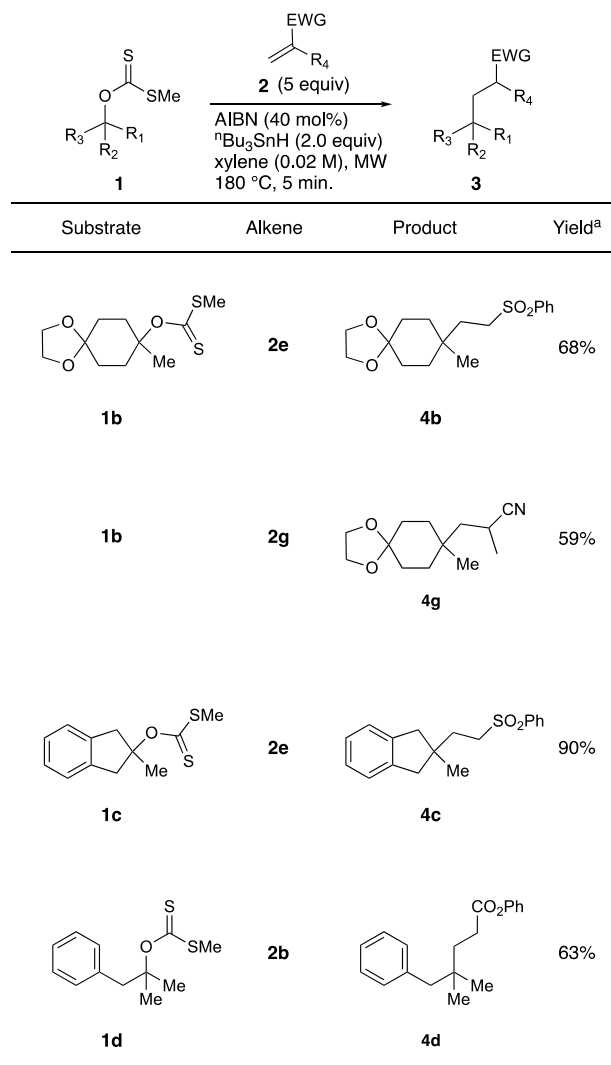


		
2b : 96% ^a	2c : 99%	2d : 99%
		
2e : 85%	2f : 64%	2g : 97%
		
2h : 71% ^a	2i : 67% ^a	2j : 22% ^a

34
35 ^aNMR yield using CHBr₃ as an internal standard.

36 Next, we investigated the tertiary xanthates (Table 3).
37 The reaction of cyclohexyl xanthate **1b** with vinyl sulfone
38 **2e** proceeded to give **4b** in 68% yield, with the quaternary
39 carbon center on the cyclohexyl ring. Although the vinyl
40 sulfone **2e** was adopted as an acceptor due to easier
41 purification of its coupling product, other alkenes were also
42 investigated for the reaction with tertiary xanthate **1b**. The
43 use of **2g** also gave the corresponding coupling product **4g**
44 in 59% yield. The reaction of five-membered analog **1c** with
45 **2e** proceeded smoothly to give **4c** in 90% yield. Next,
46 xanthates derived from acyclic tertiary alcohols were
47 examined, and the reaction of **1d** afforded desired coupling
48 product **3d** in 63% yield. Thus, our result proved that the
49 microwave-assisted tertiary carbon radical reaction is
50 applicable to not only bridgehead alcohols but also various
51 tertiary alcohols.¹³ This is the first example of the
52 intermolecular reaction of tertiary xanthates other than the
53 bridgehead xanthate with various electron deficient alkenes.

1 **Table 3.** The reaction of various tertiary xanthates **1a** with electron
 2 deficient alkenes.



3
 4 ^aIsolated yield.

5 In summary, a convenient method for tertiary carbon
 6 radical reaction was developed. Whereas tertiary carbon
 7 radicals are usually prepared from tertiary halides, we found
 8 that the microwave assists the generation and subsequent
 9 reaction of tertiary carbon radicals from tertiary xanthates.
 10 Although the steric hindrance and the Chugaev elimination
 11 sometimes interfere the preparation of tertiary xanthates,
 12 tertiary alcohols are much more readily available starting
 13 materials compared to tertiary halides. Indeed, various
 14 xanthates were prepared and reacted with various electron
 15 deficient alkenes in acceptable to good yields. As is the case
 16 of our total synthesis, this microwave-assisted tertiary
 17 carbon radical reaction will be a complementary method to
 18 the radical initiation from tertiary halides and
 19 photoactivation of tertiary oxalates for the intermolecular
 20 construction of quaternary carbon centers. Application of
 21 this microwave-assisted reaction to the total synthesis of

22 complex natural product is currently underway in our
 23 laboratory.

24
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34 Supporting Information is available on
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- 9 10 300W of microwave was irradiated under 300 psi by using
10 Discover SP (CEM Corporation).
- 11 11 Yields are basically isolated yields. However, several products
12 were difficult to completely separate from contaminants derived
13 from ⁿBu₃SnH and excess alkenes. Since repetition of silica gel
14 column chromatography afforded pure products but reduced the
15 yields, NMR yield was used for these products to clear the
16 reaction efficiency.
- 17 12 The reaction of free carboxylic acid analog also proceeded in
18 66% NMR yield. However, we did not add this alkene to Table 2
19 due to its purification problem.



- 20 66%
- 21 13 This microwave-assisted tertiary carbon radical reaction did not
22 cause the Chugaev elimination reaction, although the elimination
23 products were sometimes obtained in the preparation of tertiary
24 xanthates. After the preparation of the tertiary xanthates, the
25 Chugaev elimination is not concerned in this radical reaction.
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