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

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## 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 intermolecular reaction of tertiary carbon radicals with 13 14 electron deficient alkenes is considered to be one of the most powerful and direct method for it.<sup>1,2</sup> Tertiary carbon 15 radicals were generated from tertiary halides in many cases, 16 17 and the reactions of various halides mainly including 18 bridgehead halides with alkenes have been reported.<sup>3,4</sup> 19 However, the difficult preparation method and instability 20 are the typical drawbacks of tertiary halides to be applied in the synthesis of complex molecules. On the other hand, 21 tertiary alcohols are commercially available, readily 22 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 reactions through tertiary carbon radical.<sup>5</sup> Recently, 26 Overman et al. reported the photoredox-catalyzed 27 28 intermolecular conjugate addition reaction of electron 29 deficient alkenes with the tertiary carbon radical generated 30 from N-phthalimidoyl oxalate.<sup>6</sup> Overman and MacMillan 31 also reported another photoredox-catalyzed reaction with 32 tertiary oxalates.<sup>7</sup> These photredox-catalyzed reactions using 33 oxalates recently have attracted much attention as an alternative source of tertiary carbon radicals.8 So, in our 34 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 the intermolecular C-C bond forming reaction of tertiary 48 xanthates with electron deficient alkenes,<sup>5e</sup> whereas the 49

- 50 reaction with allyltributyltin is slightly introduced.<sup>9</sup> 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



55 (tertiary xantha

57 Scheme 1. Construction of quaternary carbon center via tertiary carbon58 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 stage of total synthesis. First, the reaction of 1a with 2a was 66 conducted by using V-40 and "Bu<sub>3</sub>SnH in toluene at 110 °C. 67 The desired C-C bond forming reaction proceeded to give 68 only 27% of 3a (entry 1). Higher reaction temperature at 69 70 140 °C slightly increased the yield to 32% (entry 2). Surprisingly, the similar reaction condition with microwave 71 (MW) irradiation<sup>10</sup> for 10 min greatly improved the yield to 72 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 (entry 8). When the amount of 2a was reduced to 2.5 equiv, 84 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**.



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<sup>a</sup>NMR yield using CHBr<sub>3</sub> as an internal standard. <sup>b</sup>The reaction was conducted in 0.075 M solution. <sup>c</sup>2.5 equiv of **2a** was used. <sup>d</sup>300W of microwave was irradiated under 300 psi.

9 Having established the efficient condition, we next 10 investigated various alkenes as the radical acceptor (Table 2).<sup>11</sup> The reactions with phenyl ester **2b** as another 11 unsaturated ester also proceeded smoothly to give C-C bond 12 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,  $\alpha$ ,  $\beta$ -unsaturated esters possessing  $\alpha$ -substituent were examined. Methyl substituent 19 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 2l 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.<sup>12</sup> 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 various33 electron deficient alkenes.



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<sup>a</sup>NMR yield using CHBr<sub>3</sub> 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.<sup>13</sup> 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 deficient alkenes.



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<sup>a</sup>Isolated 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 sometimes interfere the preparation of tertiary xanthates, 11 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 radical initiation from tertiary halides the and 19 photoactivation of tertiary oxalates for the intermolecular construction of quaternary carbon centers. Application of 20 21 this microwave-assisted reaction to the total synthesis of 22 complex natural product is currently underway in our23 laboratory.24

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35 Supporting Information is available on 36 http://dx.doi.org/10.1246/cl.\*\*\*\*\*.

### 37 References and Notes

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  - 300W of microwave was irradiated under 300 psi by using 10 Discover SP (CEM Corporation).
  - 11 Yields are basically isolated yields. However, several products were difficult to completely separate from contaminants derived from <sup>n</sup>Bu<sub>3</sub>SnH and excess alkenes. Since repetition of silica gel column chromatography afforded pure products but reduced the yields, NMR yield was used for these products to clear the reaction efficiency.
  - 12 The reaction of free carboxylic acid analog also proceeded in 66% NMR yield. However, we did not add this alkene to Table 2 due to its purification problem.

13 This microwave-assisted tertiary carbon radical reaction did not cause the Chugaev elimination reaction, although the elimination products were sometimes obtained in the preparation of tertiary xanthates. After the preparation of the tertiary xanthates, the Chugaev elimination is not concerned in this radical reaction.