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Regio- and stereoselective synthesis of methyl 5-methylenetetrahydropyran-3-carboxylates from Baylis–Hillman adducts via allyltributylstannane-mediated radical cyclization

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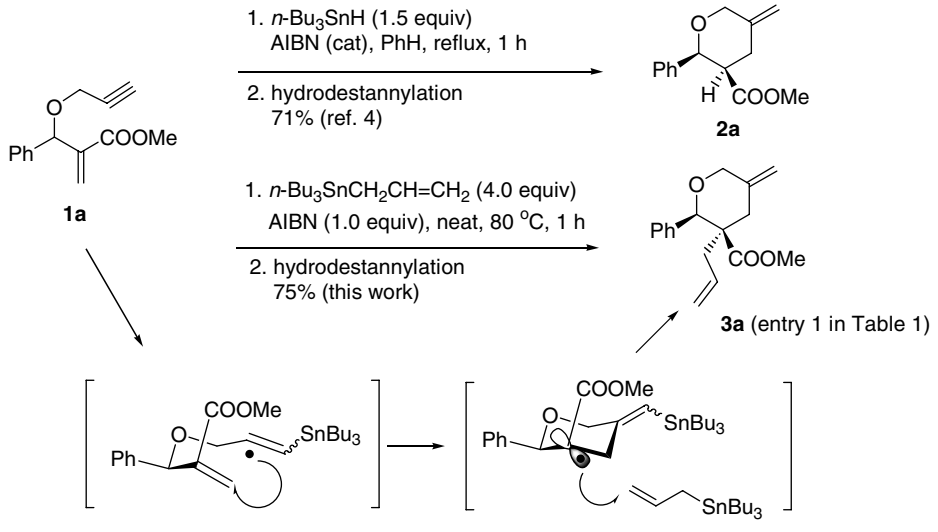
Abstract—Two types of regioisomeric methyl 5-methylenetetrahydropyran-3-carboxylate derivatives **3a**–**c** and **6a**–**c** were synthesized stereoselectively starting from the Baylis–Hillman adducts via the allyltributylstannane-mediated vinyl radical cyclization as the key step.

Radical cyclization of dienes and enynes using radical transfer reagents provides a powerful method for constructing many important carbocycles and heterocycles.[1–3] Among the radical transfer reagents, the use of *n*-Bu_3SnH has been studied extensively because of the ease of hydrogen abstraction. The use of allyltributylstannane as the radical transfer reagent has been investigated less thoroughly than *n*-Bu_3SnH presumably due to its low reactivity.[2,3] Although the reactivity of allyltributylstannane was low, the radical cyclization of



Scheme 1.

Keywords: Regioselective; Stereoselective; Methylenetetrahydropyran; Allyltributylstannane; Radical cyclization.
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enynes using this reagent can provide an interesting cyclic compounds having additional allyl group, which can be further transformed.

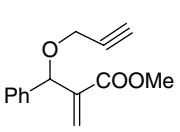
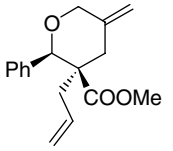
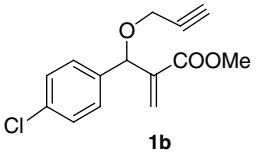
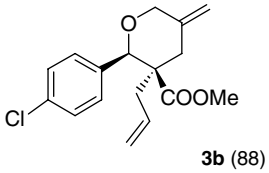
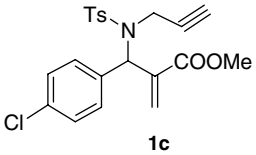
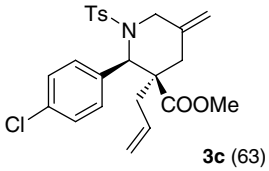
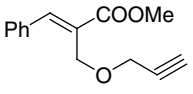
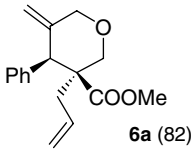
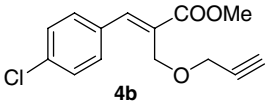
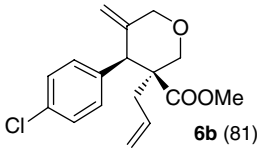
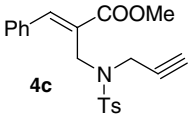
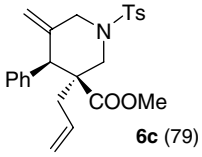
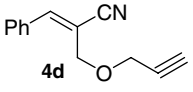
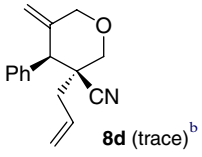
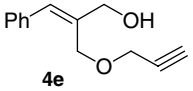
Recently Shanmugam and Rajasingh reported the synthesis of 3-methylenetetrahydropyran **2a** as shown in Scheme 1 via *n*-Bu_3SnH-mediated radical cyclization of Baylis–Hillman derivative **1a**.[4] Thus we reasoned that if we use allyltributylstannane instead of the *n*-Bu_3SnH during the radical cyclization, allyl moiety-containing methylenetetrahydropyran **3a** could be synthesized as depicted in Scheme 1.

However, the reaction of starting material **1a** and allyltributylstannane (1.5 equiv) in the presence of AIBN (10 mol%) in benzene showed very complex mixtures of products. We could not observe nor isolate any major component from the reaction mixtures, unfortunately.[2,3] After many trials, to our delight, we found that 5-methylenetetrahydropyran derivative **3a** could be formed in 75% yield when we used excess amounts of allyltributylstannane (4.0 equiv) and AIBN (1.0 equiv) without solvent at around 80 °C (Scheme 1).[5] The reaction mechanism for the selective formation of **3a** could be explained as follows:[4] (i) generation of vinyl radical at the triple bond, (ii) cyclization by the attack at the β-position of acrylate moiety, (iii) quenching with allyltributylstannane to produce **3a**. As shown in Table 1, compounds **3b** and **3c** were synthesized stereo- and regioselectively from **1b** and **1c**, respectively (entries 2 and 3 in Table 1). The stereochemistry of **3a**–**c** could be regarded as shown according to the reported paper.[4]

Recently we reported the synthesis of **5a** by *n*-Bu_3SnH-mediated radical cyclization of **4a** (Scheme 2).[6] The radical cyclization step occurred via the *5-exo-trig* mode of the corresponding alkenyl radical of **4a**. We could not obtain the *exo*-methylenetetrahydropyran derivative, which can be formed by the *6-endo-trig* mode.[6] Kinetically favored five-membered benzylic radical intermediate **A** reacted rapidly with reactive *n*-Bu_3SnH to give the product **5a** as the sole product (Scheme 2).[3a] But, when we subjected **4a** under the above reaction conditions (excess amounts of allyltributylstannane and AIBN) we obtained **6a** instead of **7a** to our surprise.

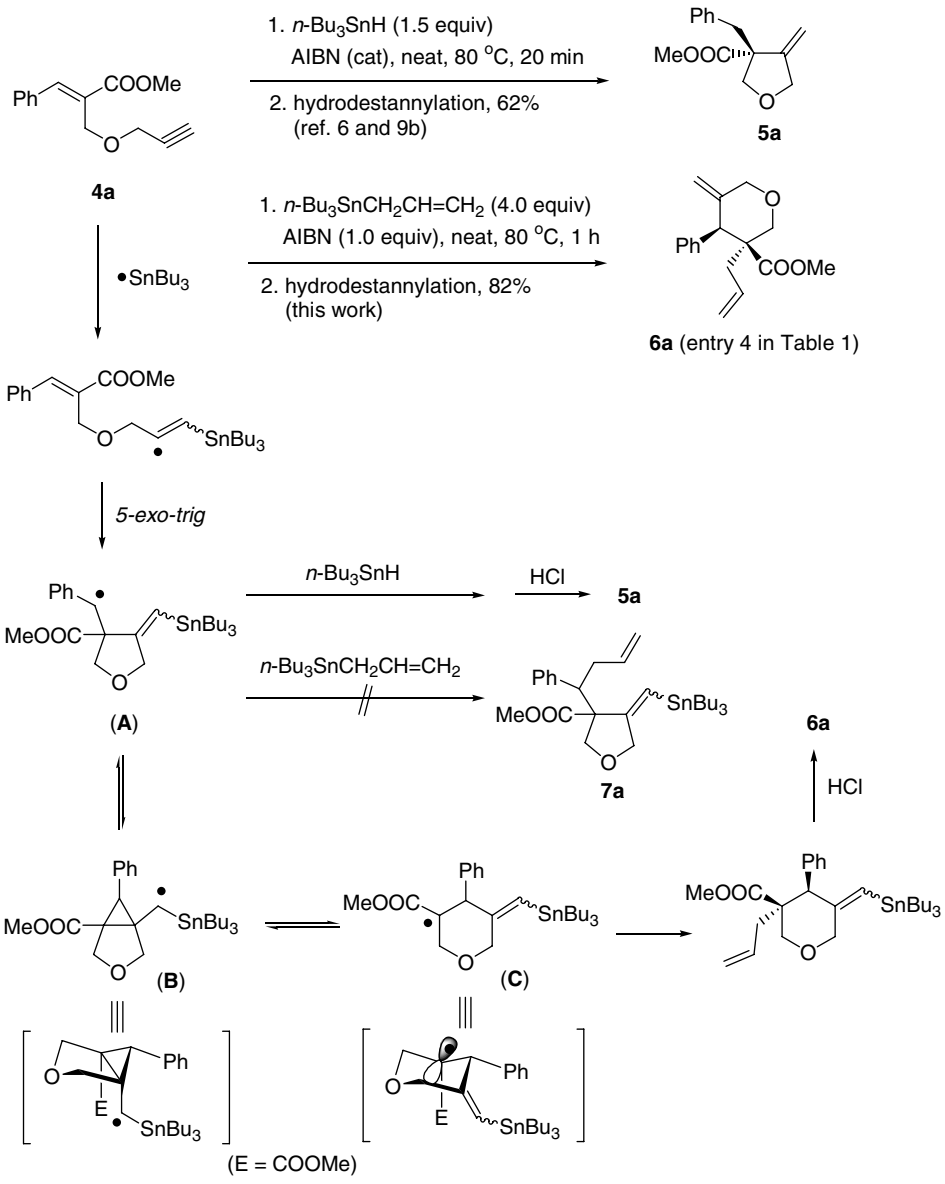
In this case, the situation was the same with the previous one (Scheme 1): that is the reaction of starting material **4a** and allyltributylstannane (1.5 equiv) in the presence of AIBN (10 mol%) in benzene showed very complex mixtures of products. When we used excess amounts of allyltributylstannane (4.0 equiv) and AIBN (1.0 equiv) in a neat condition, we obtained 5-methylenetetrahydropyran derivative **6a** in 82% yield (Scheme 2).[7] Although there were some minor spots on TLC (which could be the other isomer or simple reduction compound of the triple bond), generation of **6a** was the principle reaction pathway based on its high isolated yield. The reaction mechanism for the selective formation of **6a** could be postulated as follows: (i) generation of vinyl radical, which forms the kinetically favored five-membered intermediate **A** via the *5-exo-trig* mode, (ii) rearrangement of **A** to the six-membered radical **C** via the unstable bicyclic intermediate **B**, (iii) quenching of **C** by allyltributylstannane at the least sterically hindered side to produce **6a** after hydrodestannylation.[4] The structure of **6a** was confirmed by its NMR, IR, and MS data, and by comparison of the ^1H NMR data with

Table 1. Synthesis of regioisomeric methyl 5-methyleneterahydropyran-3-carboxylates[a]

Entry	Substrate	Product (%)
1	 **1a**	 **3a** (75)
2	 **1b**	 **3b** (88)
3	 **1c**	 **3c** (63)
4	 **4a**	 **6a** (82)
5	 **4b**	 **6b** (81)
6	 **4c**	 **6c** (79)
7	 **4d**	 **8d** (trace)[b]
8	 **4e**	Complex mixtures

[a] Conditions: (i) *n*-$Bu_3SnCH_2CH{=}CH_2$ (4.0 equiv), AIBN (1.0 equiv), neat, 80 °C, 1 h; (ii) HCl, ether, 0 °C to rt, 1 h.

[b] Starting material **4d** was recovered in 56% and trace amounts (<5%) of **6d** was isolated with some impurity (~10%).



Scheme 2.

that of the regioisomeric compound **3a**.[7] The stereochemistry of **6a** could be easily assigned by NOE experiments as shown in Figure 1. When we irradiated the benzylic proton ($\delta = 3.70$ ppm) the allylic protons and one of the *exo*-methylene protons showed 2.7% and 1.5% NOE increments, respectively.

Generation of vinyl radical might require much amount of allyltributylstannane and AIBN due to the sluggish reactivity of non-activated triple bond toward allylstannylation.[2a] The generated benzyl radical **A** could not be allylated effectively due to low reactivity of allyltributylstannane again.[3a,e] Thus the benzyl radical **A** rearranged into thermodynamically more stable six-membered radical **C**,[8] via the intermediate bicyclic radical **B**. As previously reported when we used *n*-Bu_3SnH,[6] the initial benzyl radical **A** was quenched with *n*-Bu_3SnH to form **5a** (vide supra, Scheme 2).

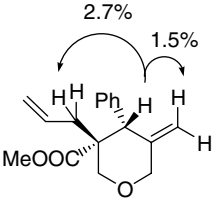


Figure 1. NOE results of **6a**.

In order to find the generality we carried out the reactions with **4b**–**e** and the results are summarized in Table 1 (entries 5–8).[6,9] From the ester moiety-containing substrates **4a**–**c** we obtained **6a**–**c** in good yields. However, we could not isolate the expected compounds from the reactions with **4d** and **4e**. The reason is not clear at this stage.

In summary, we disclosed the synthesis of regioisomeric two types of methyl 5-methylenetetrahydropyran-3-carboxylates via the allyltributylstannane-mediated radical cyclization as the key step starting from the easily

available Baylis–Hillman derivatives.[4,6] Further studies on the synthetic applications of synthesized compounds are currently underway.

Acknowledgments

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4. Shanmugam, P.; Rajasingh, P. *Synlett* **2005**, 939, and many references were cited on the importance of suitably substituted tetrahydropyran derivatives. Further references on the radical cyclization of modified Baylis–Hillman adducts were cited in Refs. 6 and 9.
5. Starting materials **1a–c** were prepared according to the reported methods[4] and identified by their spectroscopic data. Typical procedure for the synthesis of **3a** and the spectroscopic data of products **3a–c** are as follows. Typical procedure of **3a**: To a stirred solution of **1a** (230 mg, 1.0 mmol) and allyltributylstannane (1325 mg, 4.0 mmol) was added AIBN (164 mg, 1.0 mmol) and heated to 80 °C for 1 h. The reaction mixture was poured into cold ether (10 mL), treated with c-HCl (five drops), and stirred vigorously at rt for 1 h. After the usual aqueous extractive workup and flash column chromatography (hexanes/ether, 98:2) we obtained **3a** as colorless oil, 205 mg (75%).
Compound **3a**: colorless oil; 75%; IR (neat) 2957, 1732, 1454, 1209 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.18 (dd, $J = 13.5$ and 8.4 Hz, 1H), 2.31 (d, $J = 14.7$ Hz, 1H), 2.54 (ddt, $J = 13.5$, 6.3, and 1.5 Hz, 1H), 2.87 (d, $J = 14.7$ Hz, 1H), 3.48 (s, 3H), 4.14 (d, $J = 12.9$ Hz, 1H), 4.41 (d, $J = 12.9$ Hz, 1H), 4.41 (s, 1H), 4.91 (s, 1H), 4.94 (s, 1H), 5.05–5.11 (m, 2H), 5.58–5.72 (m, 1H), 7.24–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.30, 40.77, 51.06, 51.38, 71.86, 84.88, 110.27, 118.94, 127.50, 127.67, 127.92, 132.85, 138.05, 141.05, 173.03; FAB Mass 273 (M^++1).
Compound **3b**: colorless oil; 88%; IR (neat) 2949, 1730, 1086 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.16 (dd, $J = 13.5$ and 8.4 Hz, 1H), 2.28 (d, $J = 14.7$ Hz, 1H), 2.50 (ddt, $J = 13.5$, 6.0, and 1.2 Hz, 1H), 2.86 (d, $J = 14.7$ Hz, 1H), 3.49 (s, 3H), 4.13 (d, $J = 12.9$ Hz, 1H), 4.38 (s, 1H), 4.40 (d, $J = 12.9$ Hz, 1H), 4.91 (s, 1H), 4.95 (s, 1H), 5.04–5.12 (m, 2H), 5.57–5.71 (m, 1H), 7.20 (d, $J = 8.7$ Hz, 2H), 7.29 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.39, 40.76, 51.16, 51.49, 72.04, 84.28, 110.56, 119.16, 127.81, 128.88, 132.51, 133.68, 136.67, 140.69, 172.78; FAB Mass 307 (M^++1).
Compound **3c**: colorless oil; 63%; IR (neat) 2957, 1740, 1348, 1163, 1094 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.33 (s, 3H), 2.48 (d, $J = 15.3$ Hz, 1H), 2.58 (dd, $J = 14.1$ and 6.6 Hz, 1H), 2.68 (dd, $J = 14.1$ and 8.4 Hz, 1H), 2.82 (d, $J = 15.3$ Hz, 1H), 3.42 (s, 3H), 3.69–3.74 (m, 1H), 4.30 (d, $J = 14.1$ Hz, 1H), 4.97–5.12 (m, 4H), 5.17 (s, 1H), 5.47–5.61 (m, 1H), 7.01 (d, $J = 8.1$ Hz, 2H), 7.07 (d, $J = 9.0$ Hz, 2H), 7.11 (d, $J = 9.0$ Hz, 2H), 7.25 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.37, 31.12, 39.75, 47.44, 51.01, 51.69, 62.07, 114.78, 119.49, 126.99, 128.24, 129.05, 130.46, 132.17, 134.05, 135.66, 135.67, 136.45, 143.10, 172.86; FAB Mass 460 (M^++1).
6. Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 4859.
7. Starting materials **4a–e** were prepared according to the reported methods[6,9] and identified by their spectroscopic data. Spectroscopic data of products **6a–c** are as follows.
Compound **6a**: colorless oil; 81%; IR (neat) 2953, 1732, 1219, 1088 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.48 (dd, $J = 13.8$ and 7.2 Hz, 1H), 2.74 (dd, $J = 13.8$ and 7.8 Hz, 1H), 3.42 (s, 3H), 3.70 (s, 1H), 3.92 (d, $J = 12.6$ Hz, 1H), 4.16 (d, $J = 12.6$ Hz, 1H), 4.17–4.21 (m, 1H), 4.28 (d, $J = 13.2$ Hz, 1H), 5.00 (s, 2H), 5.10–5.16 (m, 2H), 5.61–5.74 (m, 1H), 7.17–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.88, 50.43, 51.20, 54.61, 65.81, 70.01, 113.95, 119.18, 126.78, 128.31, 128.35, 132.88, 140.54, 142.66, 173.59; FAB Mass 273 (M^++1).
Compound **6b**: colorless oil; 81%; IR (neat) 2949, 1732, 1499, 1225, 1096 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.46 (dd, $J = 13.5$ and 7.1 Hz, 1H), 2.70 (dd, $J = 13.5$ and 7.8 Hz, 1H), 3.45 (s, 3H), 3.67 (s, 1H), 3.90 (d, $J = 12.3$ Hz, 1H), 4.11–4.17 (m, 2H), 4.22 (d, $J = 12.9$ Hz, 1H), 4.98 (s, 1H), 5.02 (s, 1H), 5.09–5.14 (m, 2H), 5.60–5.74 (m, 1H), 7.24 (d, $J = 9.3$ Hz, 2H), 7.28 (d, $J = 9.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.86, 50.37, 51.35, 53.92, 65.96, 69.90, 114.19, 119.37, 128.45, 129.79, 132.63, 132.72, 138.99, 142.31, 173.44; FAB Mass 307 (M^++1).
Compound **6c**: colorless oil; 79%; IR (neat) 2951, 1732, 1599, 1352, 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.39–2.45 (m, 1H), 2.46 (s, 3H), 2.82 (dd, $J = 13.8$ and 7.2 Hz, 1H), 3.10 (d, $J = 12.6$ Hz, 1H), 3.18 (d, $J = 12.6$ Hz, 1H), 3.41 (s, 3H), 3.67 (s, 1H), 3.87 (d, $J = 12.9$ Hz, 1H), 4.12 (d, $J = 12.9$ Hz, 1H), 5.11–5.20 (m, 4H), 5.68–5.82 (m, 1H), 7.01–7.06 (m, 2H), 7.09–7.15 (m, 3H), 7.36 (d, $J = 8.7$ Hz, 2H), 7.71 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.53, 40.13, 44.70, 49.26, 50.36, 51.45, 54.52, 116.51, 119.92, 126.79, 127.71, 127.94, 128.30, 129.81, 132.07, 132.96, 139.80, 139.88, 143.70, 173.19; FAB Mass 426 (M^++1).
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