

## Radical Isomerization and Allylation Reactions of 2-Iodo-3,3-dimethyl-4-pentenoate Esters

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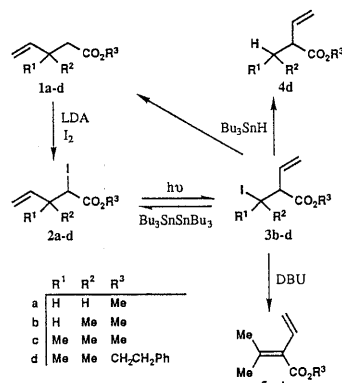
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**Abstract:** Sunlamp irradiation of methyl 2-iodo-3,3-dimethyl-4-pentenoate (2c) induces isomerization to an equilibrium mixture rich (13/1) in methyl 3-iodo-3-methyl-2-vinylbutanoate (3c). Allylations of 2c with allyl sulfides and stannanes produce mixtures of rearranged (9; 6-substituted 3-methoxycarbonyl-4,4-dimethyl-1,6-heptadienes) or unrearranged (8; 6-substituted 4-methoxycarbonyl-3,3-dimethyl-1,6-heptadienes) allylation products.

Reversible ring closures of butenyl radicals are powerful mechanistic tools,<sup>3</sup> although they have not been frequently applied in synthesis.<sup>4</sup> Such reversible closures can accomplish 1,2-vinyl shifts,<sup>5</sup> the direction of which depends on the relative stabilities of the intermediate radicals and the nature of the radical traps that are present. We felt that the atom transfer method might be useful for conducting contrathermodynamic or near-thermoneutral<sup>6</sup> isomerizations of butenyl radicals. We now report the results of preliminary experiments that partially realize this goal, and we introduce a new radical probe to determine the relative reactivity of an alkene radical trap towards two radicals of differing reactivities that are in rapid equilibrium.

Iodides 2a-d were prepared by treating the lithium enolates derived from 1a-d with I<sub>2</sub>.<sup>7</sup> Sunlamp irradiation of a benzene solution of methyl 2-iodopent-4-enoate (2a) and 10% hexabutyliditi<sup>8</sup> for 4 h resulted in no reaction other than a slow decomposition of 2a.<sup>9</sup> Irradiation of 2b under the same conditions gave 3b/2b in a ratio of 1/2.2. Continued irradiation resulted in significant decomposition, without increasing the 3b/2b ratio. Irradiation of 2c rapidly (30 min) produced 3c/2c in a ratio of about 13/1. Continued irradiation again destroyed the products without changing the 3c/2c ratio. Although we believe that this 13/1 ratio is the equilibrium value, we could not prove this because 3'-iodide 3c did not survive attempted isolation. Based on the crude <sup>1</sup>H NMR spectra of reactions conducted in C<sub>6</sub>D<sub>6</sub>, we estimated that the yield of 3c was 75-85%. There was at least one minor product in this crude reaction mixture that we could not isolate or identify.



To obtain a stable product, we treated the crude reaction mixture containing 2c with DBU. From this experiment, we isolated the volatile diene 5c<sup>10</sup> in 25% yield. By using the higher boiling substrate 2d, we considerably improved the isolated yield. Irradiation of phenethyl ester 2d either with DBU present, or followed by DBU treatment, formed diene 5d in 56-71% isolated yield.<sup>11</sup>

In another attempt to obtain a stable product, we reduced the crude reaction mixture containing 3d/2d (13/1) with Bu<sub>3</sub>SnH at 0.02M.<sup>4</sup> From this reaction, we isolated only 1d. Clearly the intermediate radicals are

returned to equilibrium under these conditions, and tributyltin hydride selectively traps the ester-substituted radical to regenerate the ultimate starting material. In an attempt to prevent re-equilibration, the crude reaction mixture containing 3d was concentrated, and 1.5 equiv of Bu<sub>3</sub>SnH was added. After heating this mixture (no solvent) for 40 min, we found that 4d was now present alongside 1d in a ratio of 2.3/1.

The results of the tin hydride experiments indicate that the equilibration of the intermediate radicals 6 and 7 is very fast. This poses synthetic difficulties. But at the same time it presents mechanistic opportunities for competitive rate studies. Nearly all competition studies of radical rates involve one radical entity competing for a pair of traps.<sup>12</sup> It is much more difficult to determine the relative reactivity of a pair of radicals competing for a single trap. In this kinetic scheme, radicals 6 and 7 are in rapid equilibrium (Figure 1). Cyclopropylcarbinyl radicals (not shown) must be intermediates in this equilibration, which occurs by reversible 3-exo cyclizations.<sup>3,4</sup> Under the isomerization conditions, we believe that the iodine atom transfer steps are reversible,<sup>6</sup> and that the observed ratio of trapped products 3c,d/4c,d (13/1) probably reflects an equilibrium value. However, hydrogen transfer from tin hydride is not reversible, so the product ratio depends on the equilibrium constant K<sub>eq</sub> and the trapping rate constants: k<sub>A</sub> and k<sub>B</sub>.<sup>13</sup>

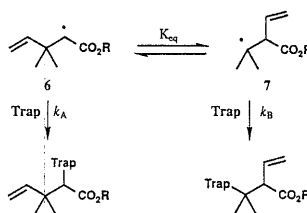


Figure 1

Radicals 6 and 7 are an especially interesting equilibrating pair because they resemble the educt and adduct radicals in a typical Giese addition reaction (Figure 2). Therefore, a knowledge of their relative reactivities is especially important. 3'-Radical 7 can be regarded as a model for a typical nucleophilic alkyl radical, which adds to an electron deficient alkene to give an ester-substituted radical resembling 6. Radicals such as 6 are classed as weakly electrophilic, perhaps ambiphilic.<sup>14</sup> The yield of a Giese reaction depends on the relative reactivities of radicals like 6 and 7 towards an electron deficient alkene and tin hydride (or a related metal hydride). Although much is known about the partitioning of radicals like 6 between addition and hydrogen transfer,<sup>12</sup> very little is known about 7.<sup>14</sup>

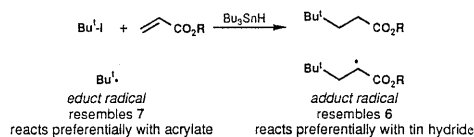
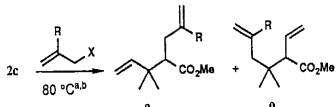


Figure 2

To confirm this analysis, we conducted several pairs of allylation experiments with a variety of allyl stannanes<sup>15</sup> and sulfides.<sup>16</sup> Table 1 summarizes the results of this series of experiments. For each entry, iodide 2c was reacted with the allylation reagent under standard conditions, and the ratio of products 8/9 was determined by <sup>1</sup>H NMR or GC analysis. Isolated yields were determined by chromatographic purification. In the

case of the sulfide precursors, isolated yields were reduced by difficulties in separating the tin and sulfur products. For each experiment in Table 1, we conducted a partner experiment by first irradiating iodide **2c** for 30 min to approach the equilibrium mixture of **3c/2c** (actual ratios were 10/1 to 13/1), and then completing the allylation under the standard conditions. In every case, the ratio of products **8/9** was identical whether we started from **2c** or **3c**. This indicates that equilibrium between **6** and **7** is rapidly established independent of the precursor.

Table 1. Allylations of **2c**



Entry	Reagent	Ratio 8/9	Yield
a	R = X = SnMe <sub>3</sub>	> 95/5	c
b	R = CH <sub>3</sub> , SnBu <sub>3</sub>	> 95/5	53%
c	R = H, X = SnBu <sub>3</sub>	91/9	60%
d	R = CO <sub>2</sub> CH <sub>3</sub> , X = SnBu <sub>3</sub>	69/31	27%
e	R = CO <sub>2</sub> CH <sub>3</sub> , X = SnPh <sub>3</sub>	63/37	65%
f	R = CH <sub>3</sub> , X = SPh	87/13	d
g	R = H, X = SPh	63/37	25%
h	R = Br, X = SPh	53/47	41%
i	R = CO <sub>2</sub> CH <sub>3</sub> , X = SPh	63/37	d

Footnotes to the Table: a) For allylstannanes: Iodide (0.2M) **1c**, stannane (1.3-1.5 equiv), and AIBN (0.1 equiv) were heated at 80°C in benzene. b) For allylsulfides: Iodide (0.2M), hexamethylditin (1.0 equiv), and allyl sulfide (3 equiv) were heated to 80°C and irradiated with a sunlamp. c) The ratio was determined after destannylation. The isolated yield was not determined. d) The products could not be separated from excess allylphenyl sulfide.

The results in Table 1 provide information on the relative reactivity of allyl stannanes and sulfides. Not surprisingly, more electron rich alkenes favor reaction with radical **6** to form **8** while more electron poor alkenes show increased reaction with radical **7** to form **9**. With comparable substitution, trialkyl allyl stannanes show a higher preference to give **8** than allyl phenyl sulfides.

These results indicate what kinds of atom transfer isomerizations of iodo esters will (and will not) be practical. 3,3-Dialkylpentenoates like **1c,d** are readily available starting from allylic alcohols by a Claisen rearrangement. Atom transfer isomerization now provides a method to convert these substrates to 3,3-disubstituted-2-vinyl-3-iodopropanoates (like **3**) and 1,1-disubstituted-2-carboalkoxybutadienes (like **5**). These results also provide some useful guidelines on the relative reactivities of the intermediate radicals involved in this isomerization. Qualitatively, equilibrating radicals **6** and **7** mimic the Giese reaction: radical **6** reacts selectively with tin hydride while radical **7** prefers electron deficient alkenes. At present, we have no quantitative information. However, we can quantitate these and related experiments (and perhaps provide further insight into the Giese reaction) provided that we can determine the equilibrium constant in Figure 1.

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- A benzene (2.5 mL) solution of **2d** (162 mg, 0.45 mmol) and hexamethylditin (9.50  $\mu$ L, 0.05 mmol) in a 10mm <sup>13</sup>C NMR tube was irradiated with a sunlamp for 30 min. The following resonances in the crude <sup>1</sup>H NMR were assigned to **3d**: (300MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  1.83 (s, 3H, CH<sub>3</sub>), 1.90 (s, 3H, CH<sub>3</sub>), 2.60 (m, 2H, OCH<sub>2</sub>CH<sub>2</sub>Ph), 3.25 d, 1H, HCCO<sub>2</sub>, H, 13 (m, 2H, OCH<sub>2</sub>CH<sub>2</sub>Ph), 4.96 (dd, 2H, CH<sub>2</sub>=), 5.90 (ddd, 1H, =CH), 7.0 (m, 5H, phenyl). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 81  $\mu$ L, 0.45 mmol) was added, and the mixture was irradiated for an additional 10 min. The reaction mixture was filtered through a short plug of silica/MgSO<sub>4</sub> and concentrated under reduced pressure. Flash chromatography (10% ether/pentane) afforded 58 mg (56%) of **5d** as a clear liquid: <sup>1</sup>H NMR (300MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  1.40 (s, 3 H, CH<sub>3</sub>), 1.62 (s, 3 H, CH<sub>3</sub>), 2.72 (t, 2 H, J = 7.07 Hz, OCH<sub>2</sub>CH<sub>2</sub>Ph), 4.31 (t, 2 H, OCH<sub>2</sub>CH<sub>2</sub>Ph), 5.05 (d, 1 H, J = 11.0 Hz, CH=CH<sub>2</sub>cis), 5.23 (d, 1 H, J = 17.5 Hz, CH=CH<sub>2</sub>trans), 6.47 (dd, 1 H, J<sub>1</sub> = 11.0 Hz, J<sub>2</sub> = 17.5 Hz, CH=CH<sub>2</sub>), 7.06 (m, 5 H, phenyl); <sup>13</sup>C (500MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  19.5, 22.8, 30.1, 35.3, 64.9, 115.1, 126.6, 127.7, 128.6, 129.2, 130.7, 131.1, 137.2, 138.2, 168.7; IR (thin film, NaCl) 3030, 2921, 1725, 1312, 1215, 1146, 700 cm<sup>-1</sup>; exact mass calcd for C<sub>15</sub>H<sub>18</sub>O<sub>2</sub>, 230.1307; found 230.1307. LRMS *m/e* 230 (5), 126 (5), 105 (100), 84 (25), 49 (35).
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