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THE REACTION OF $\boldsymbol{\beta}\text{-}\mathsf{KETOACIDS}$ WITH ALLYLBORONATES

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THE REACTION OF β -KETOACIDS WITH ALLYLBORONATES

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ABSTRACT

Allylboronates react with β -ketoacids to yield tertiary homoallylic β -hydroxycarboxylic acids. The reaction presumably proceeds via a bicyclic transition state. The β -carboxylic substituent enhances the rate of the reaction.

Allylmetallic reagents have been of synthetic, mechanistic, and biochemical importance for more than 70 years because of their well-defined stereo- and regiochemistry (1,2). Aldol condensation (3,4) and aldol-like carbon-carbon coupling reactions (5,6) have played fundamental roles in the synthesis of natural products of propiogenic/acetogenic biosynthetic origins (7). Over the last decade, the reaction of allyl- and crotyl-metal reagents with carbonyl compounds has proven to be especially important in acylic diastereoselective syntheses (8).

In earlier studies, we discovered remarkable rate and diastereoselectivity enhancements brought about by the hydroxyl group in allyl- and crotylborations involving α -hydroxyketones (9), α -oxocarboxylic acids (10,11), and

511

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KABALKA, YANG, AND WANG

 β -hydroxyaldehydes and ketones (12). These reactions are assumed to proceed via a rigid bicyclic transition state. In a study of the allylboration of β -ketoacids, we found that allylboronate **1** reacts with β -ketoacids **2** to produce tertiary homoallylic β -hydroxycarboxylic acids **3** in good yields (Tab. 1).



The allylboration of ethyl phenylacetate does not occur under the reaction conditions. The hydroxyl group in the carboxylic acid moiety evidently plays an important role. The reaction presumably proceeds through a bicyclic transition state such as 4 (Scheme 1).

Table 1. Reaction of β -Ketoacids with *B*-Allyldiisopropoxyborane

β -Ketoacids (2)		Products (3)	Yield ^a
PhCH ₂ OH	(2a)	PhCH ₂ OH O OH (3a)	65.0%
о о С ₆ Н ₁₃ ОН	(2b)	CH ₆ H ₁₃ OH O OH (3b)	79.8%
ООН	(2c)	OH O OH O(3c)	80.8%
ООН	(2d)	OH O OH (3d)	83.3%
О О О О О О О О О О О О О О О О О О О	(2-)		70.10
O O OH	(2e)	OH O UH O	/0.1%
	(2f)	OH (3f)	89.0%

^aIsolated yields.

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β -KETOACIDS WITH ALLYLBORONATES



Scheme 1. Proposed transition state of allylboration of β -Ketoacids.

Unlike other neighboring group-assisted allylborations that require Et_3N as the catalyst (9–11), preliminary investigations revealed that the allylboration of β -ketoacids can be carried out in the absence of base. In fact, the presence of Et_3N results in the decarboxylation of the β -ketoacid. A solvent study revealed that the formation of the decarboxylated product could be minimized if the reactions were run in ether or THF rather than dichloromethane.

EXPERIMENTAL

All glassware was oven-dried prior to use. Reactions were run under an inert atmosphere. ¹H and ¹³C NMR were recorded at either 250 or 300 MHz and referenced to TMS. Diisopropoxy allylboronate was prepared according to literature procedures (13).

Preparation of β -Ketoacids (2)

 β -Ketoacids were prepared according to literature procedures (14). Butyllithium (20 mmol, 12.5 mL of a 1.6 M in hexane solution) was added over 10 min to a stirred solution of bis(trimethylsilyl)malonate (20 mmol, 5.0 g) in dry ether (20 mL) under a nitrogen atmosphere at -78° C. The mixture was then allowed to warm to 0°C and a solution of the appropriate acid chloride (10 mmol) was added in one portion. The mixture was stirred for 10 min at 0°C and then shaken thoroughly with cold aqueous 5% sodium bicarbonate (50 mL) for 5–10 min. The aqueous layer was acidified to pH 1 \sim 2 with cold 4 N sulfuric acid and extracted with ethyl acetate (3 × 30 mL). The extracts were combined, dried over anhydrous magnesium sulfate, and the solvent removed under reduced pressure. The product was recrystallized from hexane.

3-Oxo-4-phenylbutanoic Acid (2a)

The reaction was carried out as described in the general procedure using phenylacetyl chloride (10 mmol, 1.6 g). The yield was 1.6 g (91%); m.p. 69°C (lit. 70°C). ¹H NMR (CDCl₃): δ 7.20–7.42 (m, 5H), 3.82 (s, 1H), 3.47 (s, 1H).

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3-Oxononanoic Acid (2b)

The reaction was carried out as described in the general procedure using heptanoyl chloride (10 mmol, 1.5 g). The yield was 1.6 g, (93%); m.p. 69.5°C (lit. 70.5°C) (15). ¹H NMR (CDCl₃): δ 3.52 (s, 1H), 2.59 (t, 2H), 1.60 (m, 2H), 1.29 (m, 6H), 0.90 (t, 3H).

4-Methyl-3-oxopentanoic Acid (2c)

The reaction was carried out as described in the general procedure using isobutyryl chloride (10 mmol, 1.1 g). The yield was 1.1 g (85%); m.p. 73°C. ¹H NMR (CDCl₃): δ 3.55 (s, 2H), 2.83 (m, 1H), 1.15 (d, 6H). Literature values: δ 3.45 (s, 2H), 2.55 (m, 1H), 1.09 (d, 6H) (16).

3-Oxo-3-*p*-toluoylpropanoic Acid (2d)

The reaction was carried out as described in the general procedure using *p*-toluoyl chloride (10 mmol, 1.6 g). The yield was 1.6 g (91%); m.p. 84.2°C (lit. 84°–86°C) (17). ¹H NMR (CDCl₃): δ 7.92 (d, 2H), 7.28 (d, 2H), 3.98 (s, 2H), 2.42 (s, 2H).

3-Cyclohexyl-3-oxopropanoic Acid (2e)

The reaction was carried out as described in the general procedure using cyclohexylcarbonyl chloride (10 mmol, 1.5 g). The yield was 1.6 g (92%); m.p. 85°C. ¹H NMR (CDCl₃): δ 3.56 (s, 2H), 2.44 (m, 1H), 1.75–1.95 (m, 4H), 1.10–1.42 (m, 6H). Literature values: δ 3.55 (s, 2H), 2.71–0.94 (m, 11H) (18).

3-Oxo-3-phenylpropanoic Acid (2f)

The reaction was carried out as described in the general procedure using benzoyl chloride (10 mmol, 1.4 g). The yield was 1.5 g (90%); m.p. 108°C (lit. 110°C) (14). ¹H NMR (CDCl₃): δ 7.98 (d, 2H), 7.45 (t, 3H), 3.98 (s, 2H).

Allylboration of β -Ketoacids—General Procedure

In a typical procedure, diisopropyl allyboronate (3 mmol in 20 mL of ether) was added to a nitrogen-flushed round-bottomed flask containing a β -ketoacid



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β -KETOACIDS WITH ALLYLBORONATES

(3 mmol) in ether (20 mL) at -10° C. The reaction was warmed to room temperature and stirred overnight. Aqueous NaHCO₃ (5%, 50 mL) was added to the reaction mixture. The aqueous layer was separated and then acidified with HCl until a pH of \sim 1 was attained. The acidified mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried over anhydrous MgSO₄, the solvent removed under reduced pressure, and the product purified by column chromatography.

3-Benzyl-3-hydroxy-5-hexenoic Acid (3a)

The reaction was carried out as described in the general procedure using 3-oxo-4-phenylbutanoic acid (**2a**) (3.0 mmol, 0.73 g). The yield was 0.41 g (65%). ¹³C (CDCl₃): δ 177.5, 136.7, 133, 130.6, 128.2, 127.0, 119.8, 73.1, 45.5, 44.0, 41.8. ¹H (CDCl₃): δ 7.25 (m, 5H), 5.92 (m, 1H), 2.9 (s, 2H), 2.5 (m, 2H), 2.28 (m, 2H). HRMS (EI) calcd for C₁₃H₁₆O₃: 220.1099; found 179.071 (M-C₃H₅).

3-Hexyl-3-hydroxy-5-hexenoic Acid (3b)

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The reaction was carried out as described in the general procedure using 3-oxononanoic acid (**2b**) (3.0 mmol, 0.52 g). The yield was 0.51 g (80%). 13 C (CDCl₃): δ 177.0, 132.5, 119.8, 73.0, 44.1, 43.0, 39.6, 32.2, 24, 23.2, 14.2. 1 H (CDCl₃): δ 5.80 (m, 1H), 5.15 (m, 2H), 2.42 (s, 2H), 2.25 (d, 2H), 1.50 (t, 2H), 1.30 (m, 8H), 0.90 (t, 3H). HRMS (EI) calcd for C₁₂H₂₂O₃: 214.1569; found 173.118 (M-C₃H₅).

3-Hydroxy-3-isopropyl-5-hexenoic Acid (3c)

The reaction was carried out as described in the general procedure using 4-methyl-3-oxopentanoic acid (**2c**) (3.0 mmol, 0.32 g). The yield was 0.42 g (81%). ¹³C (CDCl₃): δ 178.2, 132.7, 119.8, 74.4, 41.0, 40.0, 36.1, 17.2, 17.0. ¹H (CDCl₃): δ 5.91 (m, 1H), 5.17 (m, 2H), 2.45 (m, 2H), 2.27 (m, 2H), 1.92 (m, 1H), 0.98 (m, 6H). Analysis calcd for C₉H₁₆O₃: C, 62.77; H, 9.36. Found: C, 62.68; H, 9.28.

3-Hydroxy-3-p-tolyl-5-hexenoic Acid (3d)

The reaction was carried out as described in the general procedure using 3-oxo-3-*p*-tolylpropanoic acid (**2d**) (3.0 mmol, 0.53 g). The yield was 0.55 g (83%). ¹³C (CDCl₃): δ 175.5, 143, 136.2, 133.6, 129.0, 125.0, 118.5, 74.2, 48.1, 44.0, 21.6. ¹H (CDCl₃): δ 7.0–7.3 (m, 5H), 5.56 (m, 1H), 5.0 (m, 2H), 2.65 (m, 1H),

515

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KABALKA, YANG, AND WANG

2.4 (m, 1H), 2.21 (s, 2H). HRMS (EI) calcd for $C_{13}H_{16}O_3$: 220.1099; found 179.071 (M- C_3H_5).

3-Cyclohexyl-3-hydroxy-5-hexenoic Acid (3e)

The reaction was carried out as described in the general procedure using 3-cyclohexyl-3-oxopropanoic acid (**2e**) (3.0 mmol, 0.51 g). The yield was 0.42 g (70%). ¹³C (CDCl₃): δ 176.0, 134.2, 118.0, 74.2, 46.0, 42.2, 41.0, 28.0, 27.1, 26.6. ¹H (CDCl₃): δ 5.9 (m, 1H), 5.1 (m, 2H), 2.3 (m, 2H), 2.4 (m, 2H). 3.8 (m, 4H), 1.5 (m, 1H), 1,1 (m, 6H). Analysis calcd for C₁₂H₂₀O₃: C, 67.89; H, 9.50. Found: C, 67.59; H, 9.45.

3-Hydroxyl-3-phenyl-5-hexenoic Acid (3f)

The reaction was carried out as described in the general procedure using 3-oxo-3-phenylpropanoic acid (**2f**) (3.0 mmol, 0.49 g). The yield was 0.55 g (89%). ¹³C (CDCl₃): δ 177.0, 144.2, 133.0, 128.4, 127.2, 125.3, 199.8, 74.2, 47.8, 44.1. ¹H (CDCl₃): δ 7.2–7.4 (m, 5H), 5.6 (m, 1H), 5.1 (m, 2H), 2.9 (m, 2H), 2.7 (m, 2H). HRMS (EI) calcd for C₁₂H₁₄O₃ 206.0943; found 165.055 (M-C₃H₅).

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516

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517

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