

# Efficient synthesis of unsaturated branched-chain sugars in aqueous media by Heck-type reaction

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A simple and efficient method for the synthesis of unsaturated branched-chain sugars in aqueous media has been achieved using a palladium-catalyzed Heck-type reaction, and unprotected substrate can also be used in these reactions.

The palladium-catalyzed arylation and alkenylation of olefins (Heck reaction) are versatile synthetic methods for carbon-carbon bond formation and have been extensively used for organic synthesis during the past two decades.<sup>1</sup> On the other hand, the use of water as a solvent for organic reactions has attracted much attention from the viewpoints of safety, cost and environmental concerns.<sup>2</sup> Recently, some types of Heck reactions have been also performed in aqueous media. However, most of these reactions are limited to simple systems, that is, the synthesis of substituted cinnamic acid derivatives by the reaction of phenyl iodide and acrylic acid derivatives.<sup>3</sup> We report here the first example of the synthesis of branched-chain sugars in aqueous media utilizing the Heck-type reaction.

We first examined the reaction of 3,4,6-tri-*O*-acetyl-2-bromo-D-glucal (**1a**)<sup>4</sup> with methyl acrylate in the presence of a variety of palladium catalyst systems in various kinds of solvents, and we found that the use of [Pd<sub>2</sub>(dba)<sub>3</sub>·dba] (dba = dibenzylidene acetone)<sup>5</sup> as a catalyst precursor and P(*o*-tol)<sub>3</sub> as a phosphine ligand was essential to realize a highly efficient reaction (Table 1).<sup>6</sup> The reaction of **1a** with methyl acrylate using 2.5 mol% of Pd(dba)<sub>2</sub> and 5 mol% of P(*o*-tol)<sub>3</sub> in the presence of triethyl-

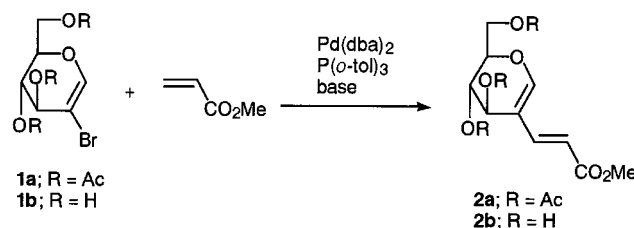
amine in CH<sub>3</sub>CN gave the product **2a** in 90% yield.<sup>†</sup> Even the use of 1 mol% Pd(dba)<sub>2</sub> afforded the product in 78% yield. The use of other solvents, such as DMF and benzene, which are commonly used in the Heck reaction, resulted in lower yield.

Then we examined the above reaction in aqueous solvent, and found the same catalyst system (Pd(dba)<sub>2</sub>-P(*o*-tol)<sub>3</sub>-Et<sub>3</sub>N) worked in both of DMF-H<sub>2</sub>O (5:1) and CH<sub>3</sub>CN-H<sub>2</sub>O (5:1) to give the product in up to 84% yield. Furthermore, the use of K<sub>2</sub>CO<sub>3</sub> instead of Et<sub>3</sub>N in the presence of *n*-Bu<sub>4</sub>NHSO<sub>4</sub> was also proved to be effective. In this system, the combination of DMF and H<sub>2</sub>O was much superior to that of CH<sub>3</sub>CN and H<sub>2</sub>O, that is, the reaction of **1a** proceeded smoothly in DMF-H<sub>2</sub>O (5:1) to afford the product **2a** in 72% yield.

One of the most characteristic features of this reaction is that the reaction can be performed with unprotected substrate. The reaction of 2-bromoglucal **1b** with methyl acrylate gave the product **2b** in 62% yield. Especially noteworthy is the operational simplicity of the reaction. Neither extractive work-up nor chromatographic purification procedure was necessary. We obtained pure product **2b** after removal of palladium catalyst by filtration through a small amount of silica gel followed by trituration with benzene.

In summary, we have developed the efficient synthesis of unsaturated branched-chain sugars in aqueous media by a Heck-type reaction, and on the basis of this method, unprotected branched-chain sugars can be prepared directly.

**Table 1** Reaction of 3,4,6-tri-*O*-acetyl-2-bromo-D-glucal (**1a**) and 2-bromo-D-glucal (**1b**) with methyl acrylate<sup>a,b</sup>



Entry	Substrate	Palladium precursor (mol%)	Base	Solvent	Conditions		
					T/°C	t/h	% yield <sup>c</sup>
1	<b>1a</b>	Pd(dba) <sub>2</sub> (1)	Et <sub>3</sub> N	CH <sub>3</sub> CN	80	80	78
2	<b>1a</b>	Pd(dba) <sub>2</sub> (2.5)	Et <sub>3</sub> N	CH <sub>3</sub> CN	60	18	90
3	<b>1a</b>	Pd(dba) <sub>2</sub> (2.5)	Et <sub>3</sub> N	CH <sub>3</sub> CN-H <sub>2</sub> O (5:1)	80	22	64
4	<b>1a</b>	Pd(dba) <sub>2</sub> (2.5)	Et <sub>3</sub> N	DMF-H <sub>2</sub> O (5:1)	80	27	64
5	<b>1a</b>	Pd(dba) <sub>2</sub> (5)	Et <sub>3</sub> N	DMF-H <sub>2</sub> O (5:1)	80	17	84
6 <sup>d</sup>	<b>1a</b>	Pd(dba) <sub>2</sub> (2.5)	K <sub>2</sub> CO <sub>3</sub>	DMF-H <sub>2</sub> O (5:1)	80	30	72
7	<b>1b</b>	Pd(dba) <sub>2</sub> (5)	Et <sub>3</sub> N	CH <sub>3</sub> CN	80	21	62

<sup>a</sup> All reactions were carried out under argon atmosphere. Two equiv. of P(*o*-tol)<sub>3</sub> per Pd was used. <sup>b</sup> Pd(dba)<sub>2</sub> was prepared according to the reported procedure (see ref. 5). <sup>c</sup> Isolated yield after silica gel column chromatography except for entry 7. <sup>d</sup> *n*-Bu<sub>4</sub>NHSO<sub>4</sub> was used as an additive.

## Experimental

### General

All melting points were uncorrected.  $^1\text{H}$  and  $^{13}\text{C}$  NMR were measured at 250 and 62.9 Hz, respectively using TMS as internal standard unless otherwise noted. Optical rotations were measured by SEPA-300 (HORIBA) in solution in a 1 dm cell. Preparative column chromatography was carried out on a Fuji-Davison BW-820 or Wacogel 300. Thin layer chromatography (TLC): Foil plates, silica gel 60 F<sub>254</sub> (Merck; layer thickness 0.2 mm). Elemental analyses were performed on a Yanaco CHN CORDER MT-5. Acetonitrile was distilled from P<sub>4</sub>O<sub>10</sub>. DMF was distilled from CaH<sub>2</sub>. Pd(OAc)<sub>2</sub> was purchased from Wako and used without further purification. [Pd<sub>2</sub>(dba)<sub>3</sub>·dba] was synthesized according to the literature.<sup>5</sup>

### Typical procedure for the reaction of 3,4,6-tri-*O*-acetyl-2-bromo-D-glucal with methyl acrylate

[Pd<sub>2</sub>(dba)<sub>3</sub>·dba] (204 mg, 0.356 mmol), P(*o*-tol)<sub>3</sub> (216 mg, 0.712 mmol) and CH<sub>3</sub>CN (2 mL) were placed under argon in an ampoule equipped with a magnetic stirring bar and a Young valve. After addition of trimethylamine (5.76 g, 57.0 mmol), the mixture was stirred for 1 h at 80 °C. 3,4,6-Tri-*O*-acetyl-2-bromo-D-glucal (**1a**) (5.0 g, 14.3 mmol) in CH<sub>3</sub>CN (8 mL), and methyl acrylate (3.85 mL, 42.8 mmol) were then added and stirred for 18 h at 80 °C. After confirmation of the completion of the reaction by TLC, the mixture was passed through a short silica gel column and the filtrate was concentrated. The residue was chromatographed on silica gel to give the product **2a** (4.6 g, 90%) as a pale yellow oil.  $R_f = 0.31$  (hexane–ethyl acetate 2:1).  $[\alpha]_D^{26} = +8.9$  ( $c = 1.0$ , CHCl<sub>3</sub>). IR (neat):  $\nu_{\text{max}}/\text{cm}^{-1}$  1742, 1629, 1491, 1443, 1369, 1231, 1167, 1029, 936, 774, 695.  $^1\text{H}$  NMR (CDCl<sub>3</sub>):  $\delta$  2.09, 2.10 (each s, 9H, OCOCH<sub>3</sub> × 3), 3.73 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 4.20 (dd,  $J_{\text{H6a-H6b}} = 7.3$  Hz,  $J_{\text{H6a-H5}} = 3.7$  Hz, 1H, H6a), 4.4–4.6 (m, 2H, H5, H6b), 5.17 (dd,  $J_{\text{H4-H3}} = 4.3$  Hz,  $J_{\text{H4-H5}} = 4.3$  Hz, 1H, H4), 5.60 (d,  $J_{\text{H3-H4}} = 4.3$  Hz, H3), 5.64 (d,  $J = 15.9$  Hz, 1H, CH=CHCO<sub>2</sub>Me), 7.00 (s, 1H, H1), 7.22 (d,  $J = 15.9$  Hz, 1H, CH=CHCO<sub>2</sub>Me).  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>):  $\delta$  20.5, 20.6, 51.3, 61.0, 62.9, 66.4, 74.4, 109.4, 113.8, 128.2, 140.9, 152.1, 167.2, 169.1, 169.7, 170.0. Anal. calcd. for C<sub>16</sub>H<sub>20</sub>O<sub>9</sub> (356.1107): C, 53.93; H, 5.66. Found: C, 53.96; H, 5.64%.

### Heck reaction in aqueous media

A mixture of anhydrous K<sub>2</sub>CO<sub>3</sub> (590 mg, 4.28 mmol), *n*-Bu<sub>4</sub>NHSO<sub>4</sub> (580 mg, 1.71 mmol), DMF (1 mL), and H<sub>2</sub>O (0.5 mL) was stirred at 20 °C for 30 min under argon in an ampoule equipped with a magnetic stirring bar and a Young valve. P(*o*-tol)<sub>3</sub> (26 mg, 0.085 mmol), 3,4,6-tri-*O*-acetyl-2-bromo-D-glucal (**1a**) (600 mg, 1.7 mmol) in DMF (1.5 mL), and methyl acrylate (0.46 mL, 5.12 mmol) were then added and stirred for another 30 min. [Pd<sub>2</sub>(dba)<sub>3</sub>·dba] (24.6 mg, 0.0427 mmol) was added and the ampoule was sealed under argon and the whole mixture was stirred at 80 °C for 30 h. After confirmation of the completion of the reaction, the mixture was passed through short silica gel and the filtrate was treated with ethyl acetate (50 mL) and brine (20 mL). The organic layer was concentrated and chromatographed on silica gel to give the product **2a** (438.2 mg, 72%) as a pale yellow oil. All spectral data are in full agreement with those of above.

### Reaction of unprotected glucal

A mixture of [Pd<sub>2</sub>(dba)<sub>3</sub>·dba] (51.0 mg, 0.088 mmol) and P(*o*-tol)<sub>3</sub> (54.0 mg, 0.18 mmol) in CH<sub>3</sub>CN (1 mL) was stirred at 20 °C for 30 min under argon in an ampoule equipped with a magnetic stirring bar and a Young valve. 2-Bromo-D-glucal (**1b**) (400 mg, 1.78 mmol) in CH<sub>3</sub>CN (1 mL), and methyl acrylate (0.48 mL, 5.34 mmol) were then added and stirred for another 30 min, and the whole mixture was stirred at 80 °C for 21 h. After confirmation of the completion of the reaction, the mixture was passed through a short silica gel column using ethyl acetate as eluent and the filtrate was concentrated. The residue was triturated with benzene to give the product **2b** (254 mg, 62%) as a colorless solid. Mp 148–153 °C.  $R_f = 0.32$  (ethyl acetate).  $[\alpha]_D^{28} = +180$  ( $c = 1.0$ , C<sub>2</sub>H<sub>5</sub>OH). IR (KBr):  $\nu_{\text{max}}/\text{cm}^{-1}$  3287, 1724, 1619, 1429, 1320, 1296, 1271, 1251, 1166, 985, 869, 782.  $^1\text{H}$  NMR ([<sup>2</sup>H<sub>6</sub>]DMSO):  $\delta$  3.63 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 3.6–3.7 (m, 3H, H5, H6a, H6b), 3.94 (dd,  $J_{\text{H4-H3}} = 4.9$  Hz,  $J_{\text{H4-H5}} = 9.8$  Hz, 1H, H4), 4.03 (d,  $J_{\text{H3-H4}} = 4.9$  Hz, 1H, H3), 4.8 (br s, 1H, OH), 5.3 (br s, 2H, 2 × OH), 5.90 (d,  $J = 15.8$  Hz, 1H, CH=CHCO<sub>2</sub>Me), 7.11 (s, 1H, H1), 7.20 (d,  $J = 15.8$  Hz, 1H, CH=CHCO<sub>2</sub>Me).  $^{13}\text{C}$  NMR ([<sup>2</sup>H<sub>6</sub>]DMSO):  $\delta$  50.8, 59.8, 64.9, 68.1, 80.8, 111.6, 113.6, 144.0, 152.2, 167.1. Anal. calcd. for C<sub>10</sub>H<sub>14</sub>O<sub>6</sub>·1/4 H<sub>2</sub>O (234.7229): C, 51.17; H, 6.22. Found: C, 51.19; H, 6.13%. The structure of **2b** was reconfirmed after derivatization to **2a** by acetylation.

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### Notes and references

† Recently, Lamberth and Bednarski reported the reaction of **1a** with methyl acrylate, acrylonitrile and styrene using the Pd(OAc)<sub>2</sub> catalyst system, however, the yields of products were moderate (39–53% yield), see ref. 6.

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