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Palladium-catalyzed stereoselective *C*-glycosidation of unprotected enones derived from D-glucal with trimethylsilyl cyanide

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Abstract

Acetylated and unprotected enones derived from D-glucal reacted with trimethylsilyl cyanide in the presence of a catalytic amount of a palladium compound in 1,4-addition fashion to afford the corresponding 3-keto-glycosyl cyanides in high yield and in high α-selectivity.

Keywords: *C*-glycosidation; enones; palladium and compounds.

Glycosyl cyanides are versatile intermediates for the synthesis of *C*-glycosyl derivatives, because the cyano group can be readily transformed into a variety of other functional groups. In fact, glycosyl cyanides have been used as the starting compounds for the synthesis of naturally occurring *C*-nucleoside antibiotics and many analogues.[1] Therefore, there have been several reports for the synthesis of *C*-glycosyl cyanides.[2] However, as for the stereoselective synthesis of 2-deoxyglycosyl cyanides, very few examples have been reported so far.[3]

The 1,5-anhydrohex-1-en-3-uloses are versatile substrates,[4] because stereoselective 1,4-addition reactions of carbon nucleophiles to the anomeric position produce the 2-deoxy-*C*-glucopyranosides after hydride reduction of the resulting ketone at the 3-position.

Here we would like to report the stereoselective synthesis of 2-deoxy-D-glucopyranosyl cyanide based on 1,4-addition of trimethylsilyl cyanide to the anomeric position of 1,5-anhydrohex-1-en-3-ulose.[5]

We recently reported the first catalytic and practical synthesis of 1,5-anhydrohex-1-en-3-uloses based on palladium-catalyzed hydrogen transfer reaction of D-glycals.[6,7] We first examined the reaction of 4,6-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*erythro*-hex-1-en-3-ulose (**1**) with trimethylsilyl cyanide in the presence of a catalytic amount of $Pd(OAc)_2$ in acetonitrile (Eq. (1)). The reaction proceeded at room temperature aided by 1 mol% of $Pd(OAc)_2$ to give 1,4-adduct (3-keto-glycosyl cyanide) after hydrolysis with 1N HCl in 89% yield (α:β=82:18). In the absence of a catalyst, only 8% yield of the product was

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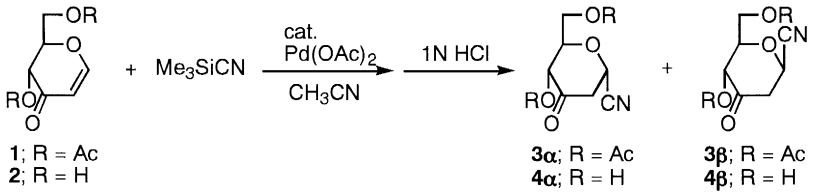
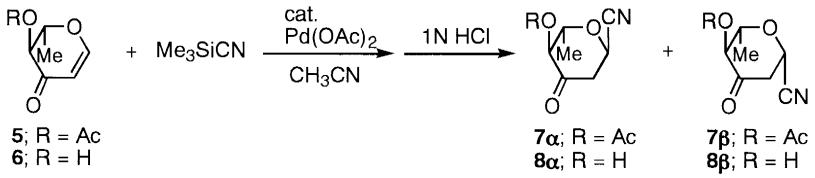
obtained after 195 h at 80°C in acetonitrile (α:β=80:20). The ratio of α:β was determined by ^{1}H NMR analysis. The results obtained are summarized in Table 1.[8] The configurations at the anomeric center of a major product and a minor one were determined as α and β, respectively, from assignment of ^{1}H NMR analysis: the coupling constant; major isomer, $J_{H1-H2ax}$=7.7 Hz, $J_{H1-H2eq}$=1.1 Hz, J_{H4-H5}=9.7 Hz; minor isomer, $J_{H1-H2ax}$=12.2 Hz, $J_{H1-H2eq}$=2.9 Hz, J_{H4-H5}=10.6 Hz, which would indicate that the major isomer has α-CN configuration and the minor one has β-CN configuration, respectively.[9] This assignment was confirmed by X-ray crystallographic analysis. The minor product **3**β was analyzed directly. The major product was analyzed after reduction of the 3-keto group with $NaBH_4$–$CeCl_3$, followed by benzoylation. The ratio of α:β was not significantly affected by temperature or the amount of $Pd(OAc)_2$. The degree of this α-selectivity was higher in the reaction of enones compared with the case of D-glucal.[3b] Furthermore, it should be mentioned that only the formation of a 1,4-addition product to the anomeric position was observed.



(1)



(2)

Table 1
Conjugate addition of trimethylsilyl cyanide to 1,5-anhydrohex-1-en-3-ulose[a]

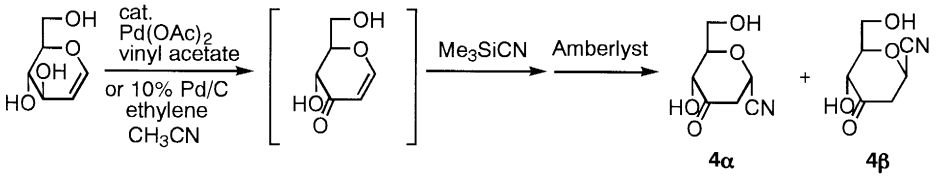
Entry	Substrate	Amount of $Pd(OAc)_2$/mol%	Conditions		Product	
			temp/°C	time/h	% yield (%)[b]	α/β[c]
1	**1**	1	25	24	89	82/18
2	**1**	1	80	12	84	77/23
3	**1**	5	80	6	89	82/18
4	**2**	1	25	2	99	92/8
5	**2**	1	80	2	96	88/12
6	**5**	1	25	13	96	76/24
7	**6**	1	25	17	98	78/22

[a] Two equiv. of Me_3SiCN was used for enone **1**, **5** and **6**, and 4 equiv. of Me_3SiCN was added for enone **2**.
[b] Isolated yield after silica-gel column chromatography. [c] ^{1}H NMR analysis.

We recently reported *C*-glycosidation of unprotected D-glucals with trimethylsilyl cyanide with the aid of a catalytic amount of $Pd(OAc)_2$ which leads to the synthesis of unprotected and unsaturated glycosyl cyanide.[3b] So we examined the reaction of unprotected enone **2** with trimethylsilyl cyanide and we found that unprotected ulose **2** was more reactive compared with acetylated enone **1**. The cyanation reaction

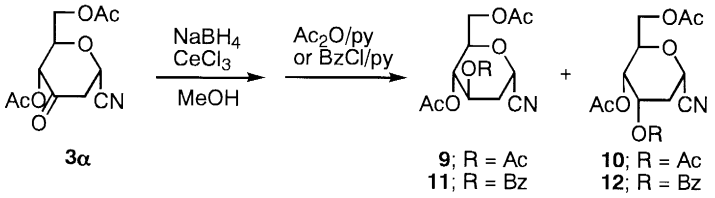
of the unprotected enone would proceed via the silylated enone, and in this case, the real cyanating reagent would be hydrogen cyanide generated by the reaction of the hydroxy group of enone and trimethylsilyl cyanide, and this hydrogen cyanide will attack the anomeric position of ulose activated by the palladium catalyst. As for the stereoselectivity of the reaction of the unprotected ulose, higher α-selectivity (88:12–92:8) was observed compared with that of the corresponding acetylated enone (77:23–82:18). In all the solvents we examined α-isomer **4**α was produced predominantly (CH_2Cl_2, 66%, α:β=86:14; Et_2O, 79%, α:β=90:10; THF, 58%, α:β=88:12). The acetylated and unprotected enones derived from L-rhamnal (**5** and **6**) were also cyanated to afford **7** and **8** in 96% and 98% yield, respectively (**7**α:**7**β=76:24, **8**α:**8**β=78:22).

Palladium(0) catalysts such as $Pd(PPh_3)_4$ and palladium on activated carbon (Pd/C) also worked as a catalyst in the cyanation reaction of **2** with trimethylsilyl cyanide ($Pd(PPh_3)_4$, 76%, α:β=85:15; Pd/C, 84%, α:β=87:13). It would be reasonable to propose that the enones are activated by these palladium compounds; however, the role of the palladium species might be different between Pd(II) species and Pd(0) species or between homogeneous system ($Pd(OAc)_2$ and $Pd(PPh_3)_4$) and heterogeneous one (Pd/C). The details are not clear at present. The observation that palladium(0) promoted the reaction effectively prompted us to attempt the synthesis of 3-keto-glycosyl cyanide in a one-pot procedure from D-glucal. After the treatment of D-glucal with 10 mol% of $Pd(OAc)_2$ in the presence of 3 equiv. of vinyl acetate (50°C, 8 h), the addition of only trimethylsilyl cyanide into the mixture resulted in the formation of 3-keto-glycosyl cyanide in 93% yield (α:β=86:14). Neither isolation of the intermediately formed enone nor additional palladium catalyst was necessary to obtain **4**α and **4**β (Eq. (3)). This one-pot procedure was also carried out by using the Pd/C–ethylene system. That is, treatment of D-glucal with 10 weight% of 10% Pd/C under ethylene atmosphere (50°C, 13 h), followed by the addition of trimethylsilyl cyanide produced 3-keto-glycosyl cyanide in 84% yield (α:β=91:9) after 25 h at room temperature. In these reactions, vinyl acetate and ethylene obviously facilitated the reaction of the first step of the catalytic hydrogen transfer reaction of D-glucal to enone as sacrificial hydrogen acceptors.



(3)

The 3-keto group in **3**α was reduced by the treatment of $NaBH_4$–$CeCl_3$ followed by acetylation to afford **9** and **10** in 78% yield (**9**:**10**=74:26) (Eq. (4)).



(4)

In summary, acetylated and unprotected enones derived from D-glucal reacted with trimethylsilyl cyanide in the presence of a catalytic amount (1 mol%) of $Pd(OAc)_2$ to afford the 3-keto glycosyl cyanides in high yield and in high α-selectivity.

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8. A typical procedure is as follows (entry 1 in Table 1): 4,6-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*erythro*-hex-1-en-3-ulose (**1**) (3.38 g, 14.8 mmol), MeCN (6 mL) and trimethylsilyl cyanide (3.95 mL, 29.6 mmol) were placed under argon in an ampoule equipped with a magnetic stirring bar and a Young valve. After addition of $Pd(OAc)_2$ (33.2 mg, 0.15 mmol), the mixture was stirred for 24 h at 25°C. The completion of the reaction was confirmed by TLC, then the mixture was poured into 1N HCl solution. Extraction with ethyl acetate (50 mL×5) and concentration afforded the crude product, which was chromatographed on silica gel to give a mixture of **3**α and **3**β (3.1 g, 89%) in a ratio of α:β=82:18. Compound **3**α: mp 59–61°C. $[\alpha]_D$=112.5 (*c*=1.0, $CHCl_3$). IR (neat): ν_{max} (cm^{-1}) 2968, 2929, 2376, 1743, 1432, 1376, 1242, 1210, 1164, 1095, 1057, 1015, 975, 905, 751. ^{1}H NMR ($CDCl_3$) δ 2.13, 2.21 (each s, 6H, COCH_3×2), 2.83 (dd, $J_{H2eq–H2ax}$=14.9 Hz, $J_{H2eq–H1}$=1.1 Hz, 1H, H_{2eq}), 3.12 (ddd, $J_{H2ax–H2eq}$=14.9 Hz, $J_{H2ax–H1}$=7.7 Hz, $J_{H2ax–H4}$=0.9 Hz, 1H, H_{2ax}), 4.3–4.4 (m, 3H, H_5, H_6, $H_{6'}$), 5.25 (dd, $J_{H1–H2ax}$=7.7 Hz, $J_{H1–H2eq}$=1.1 Hz, 1H, H_{1eq}), 5.26 (d, $J_{H4–H5}$=9.7 Hz, 1H, H_4). ^{13}C NMR ($CDCl_3$) δ 19.9, 20.2 (CO*C*H_3×2), 43.0 (C-2), 61.5 (C-6), 64.2 (C-1), 72.2 (C-4), 75.3 (C-5), 114.8 (CN), 168.7, 169.9 (*C*OCH$_3$×2), 195.0 (C=O). Anal. calcd for $C_{11}H_{13}NO_6$: C, 51.77; H, 5.13; N, 5.49. Found: C, 51.60; H, 5.02; N, 5.48. Compound **3**β: mp 92–94°C. $[\alpha]_D$=+105.9 (*c*=1.0, $CHCl_3$). IR (neat): ν_{max} (cm^{-1}) 2994, 2960, 2936, 2900, 2364, 1747, 1739, 1442, 1419, 1369, 1273, 1233, 1227, 1214, 1167, 1111, 1088, 1066, 1044, 978, 919, 888, 882, 707. ^{1}H NMR ($CDCl_3$) δ 2.14, 2.18 (each s, 6H, COCH_3×2), 2.94 (dd, $J_{H2eq–H2ax}$=14.6 Hz, $J_{H2eq–H1}$=2.9 Hz, 1H, H_{2eq}), 3.10 (ddd, $J_{H2ax–H2eq}$=14.6 Hz, $J_{H2ax–H1ax}$=12.2 Hz, $J_{H2ax–H4}$=0.9 Hz, 1H, H_{2ax}), 3.94 (ddd, $J_{H5–H4}$=10.6 Hz, $J_{H5–H6}$=4.0 Hz, $J_{H5–H6'}$=2.8 Hz, 1H, H_5), 4.3–4.35 (m, 2H, H_6, $H_{6'}$), 4.58 (dd, $J_{H1–H2ax}$=12.2 Hz, $J_{H1–H2eq}$=2.9 Hz, 1H, H_1), 5.19 (d, $J_{H4–H5}$=10.6 Hz, 1H, H_4). ^{13}C NMR ($CDCl_3$) δ 19.9, 20.2 (CO*C*H_3×2), 43.7 (C-2), 61.8 (C-6), 64.0 (C-1), 72.3 (C-4), 76.5 (C-5), 115.1 (CN), 168.7, 170.0 (*C*OCH$_3$×2), 195.3 (C=O). Anal. calcd for $C_{11}H_{13}NO_6$: C, 51.77; H, 5.13; N, 5.49. Found: C, 51.73; H, 5.09; N, 5.45.
9. Tatsuta et al. reported that β-cyanide was obtained as a single isomer in the reaction of 1,5-anhydrohex-1-en-3-ulose **1** with acetone cyanohydrin and Hünig's base (Ref. 5a). They did not isolate the β-cyano ketone, but reduced the 3-keto group to alcohol with $NaBH_4$–$CeCl_3$, followed by acetylation to obtain **9** and **10**. The ^{1}H NMR spectrum of this product **9** was fully identical to our main product after reduction and acetylation from **3**α. We determined **3**α as α-isomer from ^{1}H NMR and X-ray crystallographic analyses of 3-benzoyl derivatives **11**.