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C-Glycosidation of Unprotected D-Glycals with Trimethylsilyl Cyanide

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Abstract
Unprotected glycals smoothly react with trimethylsilyl cyanide in the presence of a catalytic amount of $Pd(OAc)_2$ to yield the corresponding unprotected glycosyl cyanides in high yield.

Keywords: glycals, glycosidation, palladium and compounds, cyanides

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 starting compounds for the synthesis of naturally occurring C-nucleoside antibiotics and many analogues [1]. Therefore, there have been some reports for the synthesis of C-glycosyl cyanides [2]; however, all reported procedures use a protected substrate, namely, acetylated, benzylated, and benzoylated, or acetal glycosyl sugars. Here we would like to report the first example of the reaction of unprotected glycals with trimethylsilyl cyanide (Me_3SiCN) with the aid of a small amount of a palladium catalyst which leads to the synthesis of unsaturated unprotected glycosyl cyanides [3].

In connection with our research on the synthesis of unprotected branched-chain sugars, we examined the C-glycosidation of unprotected 2-substituted glycals with Me_3SiCN. After screening of a variety of catalysts, we found that both 3,4,6-O-acetyl and unprotected D-glucal (**1** and **3**) were smoothly coupled with Me_3SiCN by using 1 mol% of $Pd(OAc)_2$ in CH_3CN to afford the corresponding 2,3-unsaturated glycosyl cyanide **8** and **10** in 95% and 99% yield, respectively [4]. Furthermore, various glucals bearing substituents at the 2-position (**4**–**7**) also reacted with Me_3SiCN in the presence of 1–10 mol% of $Pd(OAc)_2$ to afford the corresponding unsaturated glycosyl cyanides in satisfactory yields (Table 1) [5,6]. Compounds **6** and **7** were prepared by the reaction of the corresponding 2-bromoglucal (**4** and **5**) and methyl acrylate by palladium-catalyzed Heck reaction [7].

As for the stereochemistry of the reaction, moderate to high α-stereoselectivity was observed in the reaction of unprotected glycals. On the other hand, only a low level of selectivity was attained in the reaction of the acetylated glycals, though the acetylated glycals exhibited higher reactivity. Especially, high α/β selectivity was attained ($\alpha/\beta > 98/2$) for the reaction of unprotected 2-bromoglucal (**5**), whereas the corresponding tri-O-acetyl-2-bromoglucal (**4**) afforded only poor selectivity ($\alpha/\beta = 55/45$).

The cyanation reaction of unprotected glucals would proceed *via* silylated glucals. For a relatively sluggish substrate (**5** and **7**), silylation with Me_3SiCN took place much faster than

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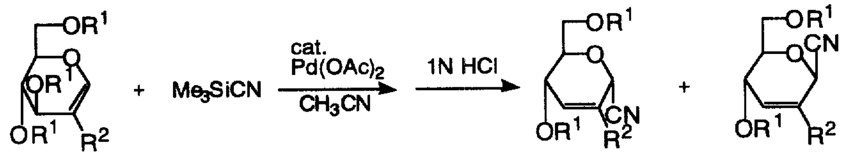
Table 1. *C*-Glycosidation of protected and unprotected D-glycals with Me_3SiCN catalyzed by $Pd(OAc)_2$[a]



1—7

8—14

Run	Substrate	$Pd(OAc)_2$ /mol%	Temp/°C	Time/h	Product	yield (%)[b]	α/β[c]
1	**1** (R^1 = Ac, R^2 = H)	1	20	3	**8**	95	58/42
2	**2** (R^1 = $SiMe_3$, R^2 = H)	1	80	48	**9**	82	75/25
3	**3** (R^1 = H, R^2 = H)	1	80	24	**10**	99	75/25
4	**4** (R^1 = Ac, R^2 = Br)	1	80	6	**11**	85	55/45
5	**5** (R^1 = H, R^2 = Br)	5	80	96	**12**	90	>98/2
6	**6** (R^1 = Ac, R^2 = (*E*)-$CH=CHCO_2Me$)	1	80	24	**13**	92	60/40
7	**7** (R^1 = H, R^2 = (*E*)-$CH=CHCO_2Me$)	10	80	60	**14**	97	65/35

[a] Two equiv. of Me_3SiCN was used for protected glycals (**1**, **2**, **4** and **6**) and 5 equiv. of Me_3SiCN was added for unprotected glycals (**3**, **5**, and **7**). [b] Isolated yield after silica-gel column chromatography. Silylated products were hydrolyzed with 1N HCl. When the reaction mixtures were treated with a mixture of satd. $NaHCO_3$ solution and a few drops of pyridine, silylated products were obtained (run 3,5 and 7). [c] ^1H NMR analysis.

cyanation. In the case of **3**, both the silylation and cyanation proceed rapidly, so we prepared silylated materials **2** independently to use as a substrate. The α/β ratio of the products indicates that the cyanation would proceed *via* silylation. When unprotected substrates were used, the real cyanating reagent would be hydrogen cyanide generated by the reaction of the hydroxy group of glucals and Me_3SiCN, and this hydrogen cyanide will attack the anomeric position of glucals activated by $Pd(OAc)_2$.

In conclusion, in the presence of a catalytic amount of $Pd(OAc)_2$, unprotected glucals including 2-substituted ones were coupled with Me_3SiCN to afford the corresponding unsaturated glycosyl cyanides in high yield.

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[1] Levy DE, Tang C, "The Chemistry of *C*-Glycosides", Pergamon. Chapt.2, 1995.

[2] De las Heras FG, San Felix A, F-Resa P. Tetrahedron 1983; 39: 1617–1620. Drew KN, Gross PH. J. Org. Chem. 1991; 56:509–513. Raadt A, Griengl H, Klempier N, Stütz AE, J. Org. Chem, 1993; 58:3179–3184, and references cited therein.

[3] Recently, Toshima and co-workers reported the reaction of unprotected glycals with allyltrimethylsilane using an equimolar amount of trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf). Toshima K, Ishizuka T, Matsuo G, Nakata M, Tetrahedron Lett. 1994; 35, 5673–5676. Toshima K, Matsuo G, Ishizuka T, Ushiki Y, Nakata M, Matsumura M, J. Org. Chem. 1998; 63: 2307–2313.

[4] Deacetylation of **8** to **10** by standard method (NaOMe/MeOH, K_2CO_3/MeOH, $Ba(OH)_2/H_2O$) was not always successful, because the addition of methanol to the cyano group giving the corresponding imidate occurred. See, Somasák L. Carbohydr. Res. 1996; 286:167–171. Poonian MS, Nowoswiat EF, J. Org. Chem. 1980; 45: 203–208, and references cited therein.

[5] A typical experimental procedure is as follows: In an ampoule equipped with a magnetic stirring bar were placed 2-bromoglucal (**5**) (306 mg, 1.36 mmol) and CH_3CN (2 mL) under argon atmosphere. After addition of Me_3SiCN (0.9 mL, 6.8 mmol) and $Pd(OAc)_2$ (15.5 mg, 0.07 mmol), the mixture was stirred for 96 h at 80 °C. After confirmation of the completion of the reaction by TLC, the mixture was poured into 1N HCl (30 mL) and extracted with ethyl acetate (20 mL x 5). The combined organic layer was washed with satd. $NaHCO_3$ (20 mL) and brine (20 mL), and dried with anhydrous Na_2SO_4 then evaporated. The residue was chromatograped on silica-gel to give the product **12** (286 mg, 90%) as a pale yellow oil. $[\alpha]_D^{25}$ +3.6 (*c* 1.0, EtOH). Acetylated compound **11**; $[\alpha]_D^{29}$ +58.4 (*c* 1.0, $CHCl_3$).

[6] A Pd(0) species such as $Pd(PPh_3)_4$ did not work as a catalyst.

[7] Hayashi M, Amano K, Tsukada K, Lamberth C, submitted for publication.