Synthesis of Pyranopyridines: LiCl Mediated Palladium-Catalyzed Cyclization of Iodo-(3-butenyloxy)pyridines

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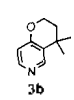
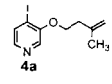
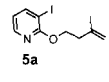
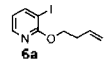
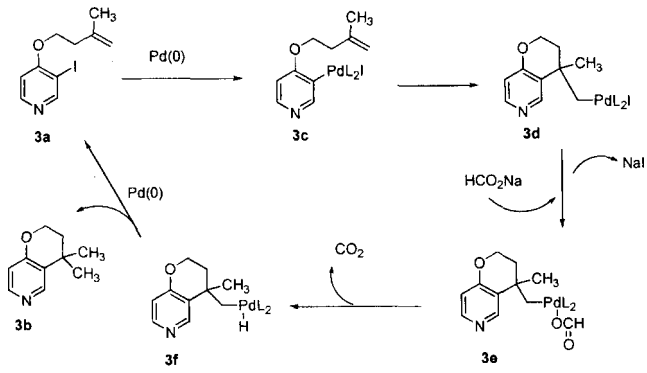
Pyranopyridines are important intermediates in the synthesis of biologically active compounds[1] and chemically interesting molecules due to their structural similarity to quinolines, substituted pyridines, and benzopyrans.[2] However, the reported synthetic methods of pyranopyridines need high reaction temperature[3] or highly functionalized pyridine derivatives[4] which can not be easily prepared. Although electrophilic cyclization of carbocyclic aromatics proceeds smoothly in thermal reactions, the cyclization of nitrogen containing heteroaromatics meets with some difficulties due to π-electron deficiency of the rings. Recently, palladium-catalyzed cyclization of olefins containing aryl or alkenyl halide has been widely applied to synthesize various heterocycles which could not be easily synthesized by conventional methods.[5] However, little attention has been paid to the synthesis of fused pyridine derivatives by Heck reaction due to possible formation of π-allyl complexes or metal complex with pyridine derivatives.

We now report first transition metal approach to synthesize pyranopyridines under LiCl mediated palladium-catalyzed cyclization of iodo-(3-butenyloxy)pyridines. The iodo-(3-butenyloxy)pyridine derivatives were prepared by literature procedures.[6a,7] Previously reported palladium-catalyzed intramolecular cyclization to furopyridines showed that the palladium-catalyzed intramolecular cyclization of allyloxy-iodopyridines gave low yields of desired products with *n*-Bu_4NCl.[6] From our previous results, the palladium-catalyzed cyclization reactions using LiCl instead of *n*-Bu_4NCl needed higher reaction temperature and longer reaction time, but clean products were obtained with a easy work-up process. LiCl mediated palladium-catalyzed cyclization[8] of iodo-(3-butenyloxy)pyridines was applied to avoid formation of π-allyl palladium complexes by sequential migration of double bond. The results of LiCl mediated palladium-catalyzed cyclization of iodo-(3-butenyloxy)pyridines are summarized in Table 1. Optimium yields of pyranopyridines were obtained under standard reaction conditions [5% $Pd(OAc)_2$, 1 eq. LiCl, 2 eq. HCO_2Na, 2 eq. base, DMF, 100 °C, 8 h]. From the experimental results, there seemed to be little or no difference in overall yields. However, the isomeric ratio of **1b** and **1c** was quite dependant on added base (entries 1-3). The reaction without sodium formate provided more **1c** due to less favorable formation of palladium hydride intermediate. The reaction using Ag_2CO_3 as a base provided the non-isomerized product predominantly. Presumably, the Ag^+ promotes reductive elimination of palladium for the catalytic cycles. The reaction of 2-cyano-3-iodo-4-(3-butenyloxy)pyridine also examined under same reaction conditions (entry 4). Two isomeric products (**2b** and **2c**) were obtained in the ratio of 2 : 1. The cyano substituted pyranopyridines (**2b** and **2c**) could be transformed carboxylic acid, amide and esters. We also investigated the reaction of 3-iodo-4-(3-methyl-3-butenyloxy)pyridine (**3a**) under various conditions. The reaction using ammonium formate instead of sodium formate provided 10% lower yield of cyclized product **3b** (entries 5-6). However, only starting substrate was recovered in the reaction without sodium formate (entry 8). The cyclization of 3-iodo-4-(3-methyl-3-butenyloxy)pyridine (**3a**)

Table 1. LiCl-mediated palladium-catalyzed intramolecular cyclization of iodo-(3-butenyloxy)pyridines

Entry[a]	Substrate	Base	Products		Isolated yield (%)	Isomer ratio (**b**:**c**)[b]
1	 **1a**	Na_2CO_3	 **1b**	 **1c**	76	3.2
2[c]	**1a**	Na_2CO_3	**1b**	**1c**	74	1.3
3	**1a**	Ag_2CO_3	**1b**	**1c**	75	1:4
4	 **2a**	Na_2CO_3	 **2b**	 **2c**	76	2:1
5	 **3a**	Na_2CO_3	 **3b**		83	
6[d]	**3a**	Na_2CO_3	**3b**		73	
7	**3a**	K_2CO_3	**3b**		75	
8[c,e]	**3a**	Na_2CO_3	**3b**		-	
9	 **4a**	Na_2CO_3	 **4b**		60	
10	 **5a**	Na_2CO_3	 **5b**		83	
11	 **6a**	Na_2CO_3	 **6b**	 **6c**	80	2:1

[a]All reactions were run on a 0.5 mmol scale. [b]The isomer ratio was determined by ^1H NMR spectroscopy. [c]The reaction was run without HCO_2Na. [d]HCO_2NH_4 was used instead of HCO_2Na. [e]Only starting material was recovered.



Scheme 1

is quite interesting, since the substrate failed to react without formate salt, but a good yield of the pyranopyridines were obtained in the presence of 2 eq. sodium formate. Other reactions using-iodo-3-(3-methyl-3-butenyloxy)pyridine (**4a**) and 3-iodo-2-(3-methyl-3-butenyloxy)pyridine (**5a**) provided **4b** and **5b** with reasonable yields (entries 9-10). Finally, we examined the reaction of 3-iodo-2-(3-butenyloxy) pyridine. The reaction also provided **6b** and **6c** in the ratio of 2 : 1 (entry 11).

The palladium-catayzed cyclization mechanism of 3-iodo-4-(3-methyl-3-butenyloxy)pyridine (**3a**) presumably proceeds as in Scheme 1. The $Pd(OAc)_2$ could be reduced to Pd(0) under reaction conditions. The **3c** could be formed by oxidative addition of Pd(0) to **3a**. The intramolecular cyclization of intermediate **3c** would form cyclic intermediate **3d**. Addition of sodium formate to **3d** would give formate complexes **3e** which would decompose to hydride complexes **3f**.[9] The intramolecular hydride attack of **3f** proceeds from the palladium side to give the product **3b** and Pd(0).

In summary, the LiCl mediated palladium-catalyzed cyclization is very useful synthetic method to prepare pyranopyridine derivatives.[10] Analogs of omeprazole (a proton pump inhibitor used as anti-ulcerant) were prepared with the derivatives of present pyranopyridines. The analogs were very effective proton pump inhibitiors *in vitro*.[11] The use of present pyranopyridines[12] in the synthesis of other biologically-active compounds are in progress.

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12. General procedure for the synthesis of pyranopyridine *via* LiCl mediated palladium-catalyzed cyclization: Synthesis of **3b**. To a 10-mL vial containing a magnetic stirring bar was added the following reagents: $Pd(OAc)_2$ (0.025 mmol), Na_2CO_3 (1.0 mmol), HCO_2Na (1.0 mmol), LiCl (0.5 mmol), 3-iodo-4-(3-methyl-3-butenyloxy)pyridine (**3a**) (0.5 mmol), and 5 mL of DMF. The reaction mixture was stirred at 100 °C for 8 h. The mixture was diluted with ether (30 mL) and washed with saturated aqueous NH_4Cl (2×20 mL). The ether layer was dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography using hexane/ethyl acetate. 4,4-Dimethyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]pyridine (**3b**) was obtained as a yellow oil in 83% isolated yield: ^{1}H NMR ($CDCl_3$, 200 MHz) 8.40 (s, 1H, ArH), 8.17 (d, 1H, J = 5.6 Hz, ArH), 6.70 (d, 1H, J = 5.6 Hz, ArH), 4.25 (td, 2H, J = 4.3, 1.4 Hz, CH_2), 1.83 (td, 2H, J = 4.3, 1.4 Hz, CH_2), 1.38 (s, 6H, CH_3); MS(EI) *m/z* 163 (M^+, 29.6), 148 (100), 133 (26.4), 120 (9.7), 84 (36.3), 43(8.4).