Preparation of β-Heteroaryl Carbonyl Derivatives *via* LiCl-mediated Heck Reaction

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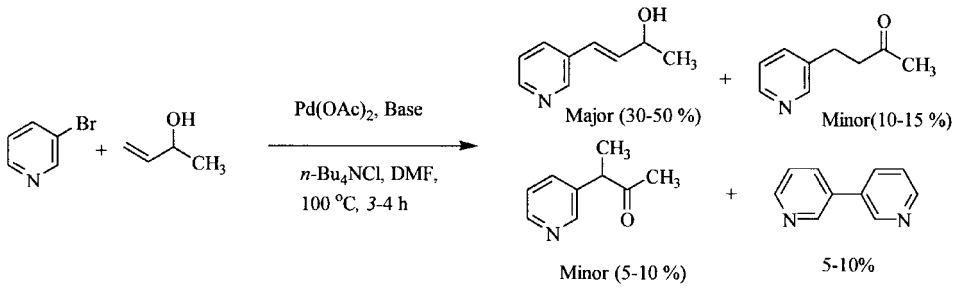
The palladium-catalyzed carbon-carbon coupling of aryl halides with alkenes, generally known as the Heck reaction, provides elegant and highly convergent routes to structurally complex molecules.[1] In spite of usefulness for arylation to alkenes, the reaction with unsymmetric alkenes frequently encountered low regioselectivity or isomerization of products.[2] When allylic alcohols are used as an alkene component for coupling with aryl halides, the regioselectivity and isomerization of products could be controlled by specific variation of components in catalytic systems.[3-6] Thus, aryl ketone compounds can be obtained by variation of reaction conditions. However, there are only a few reports on the palladium-catalyzed heteroarylation of allylic alcohol to synthesize heteroaryl carbonyl compounds,[7-10] which are key intermediates in organic synthesis.[11-13] The limited applications to heterocycles prompted us to explore the palladium-catalyzed heteroarylation of allylic alcohols with various heterocycles.

Results and Discussions

The preparation of β-pyridyl ketones was previously reported without chloride sources, but the reactions gave complex mixtures of several products with limited heteroaromatics after a long reaction time.[9-10] Initially, we examined the reaction of 3-bromopyridine with 3-buten-2-ol under *n*-Bu_4NCl-mediated palladium-catalyzed reaction conditions[1,2] to overcome the difficulty. Unfortunately, the reaction using *n*-Bu_4NCl with base (KOAc, K_2CO_3, NaOAc, or Et_3N) provided a mixture of several products (Scheme 1).

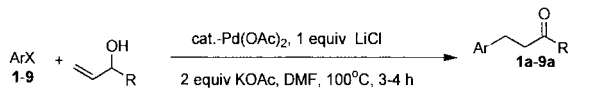
The unique ability of palladium to migrate along carbon chains could be controlled with variation of reaction conditions.[1,2] So we examined the reactions using LiCl[14] instead of *n*-Bu_4NCl as a chloride source with various bases for selective formation of β-pyridyl ketones. The optimum yield of desired 4-(3-pyridyl)-2-butanone was obtained with KOAc as a base. We investigated various heteroaryl halides with primary and secondary allylic alcohols under optimized reaction conditions. The results are summarized in Table 1. Since oxidative palladium addition to halopyridines is largely dependent on their substituent or position, we examined the palladium-catalyzed reaction with various 3 or 4-halopyridines. In general, the reactions proceed very well with either electron-donating or electron-withdrawing substituents on halopyridines. The desired β-pyridyl ketone was obtained as a major product with trace amount of heteroaryl substituted allyl alcohol and α-heteroaryl ketone (entries 1, 3, 5, 6, 7). On the other hand, the best yields of β-heteroaryl aldehydes were obtained with Et_3N as a base instead of KOAc (entry 2 and 4). We also examined two nitrogen containing pyrazole bromide (entry 8). The reaction provided resonable yields of desired ketone with protected pyrazole, but the unprotected pyrazole bromide did not proceed through present method. The aryl iodide substituted with protected tetrazole also provided desired ketone in 65% yield. Finally, the methyl 5-iodofuroate was treated under optimum condition to give methyl 4-(3-oxobutyl)-2-furoate in 61% yields.

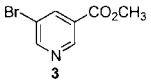
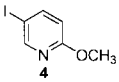
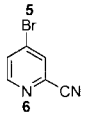
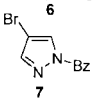
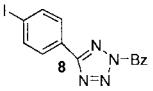
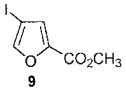
The formation of β-heteroaryl carbonyl compound can be explained by following possible mechanism (Scheme 2). The $Pd(OAc)_2$ is reduced to palladium(0) in the presence of the olefin. The palladium(0) complex reacts with heteroaryl halide *via* oxidative addition. The heteroaryl palladium complex adds to double bond of the allylic alcohol in a syn fashion. Subsequent faster or more selective β-hydride elimination resulted in intermediate leading to enol. Similarly, elimination to give allylic alcohol followed by readdition of the hydridopalladium species to the double bond and subse-



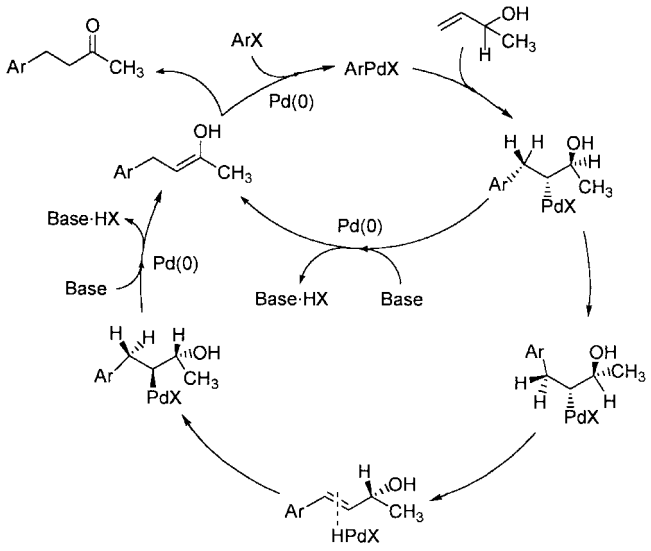
Scheme 1

Table 1. Palladium-catalyzed Heteroarylation of Allylic alcohols



Entry	Heteroaryl halide	R	Product	Isolate yields (%)[a,b]
1		CH_3	**1a**	75
2		H	**1b**	52[c]
3		CH_3	**2a**	60
4		H	**3a**	45[c]
5		CH_3	**4a**	63
6		"	**5a**	54
7		"	**6a**	60
8		"	**7a**	72
9		"	**8a**	65
10		"	**9a**	61

[a]All reactions were carried out under standard reaction conditions (0.5 mmol heteroaryl halide, 1.0 mmol allylic alcohol, 5 mol% $Pd(OAc)_2$, 0.5 mmol LiCl, 1.0 mmol KOAc in DMF (5 mL) at 100 °C for 3-4 h. [b]Less than 5% mixture (substituted allylic alcohol and α-heteroaromatic ketone) was obtained. [c]The reaction used Et_3N in stead of KOAc as a base.



Scheme 2

quent β-hydride elimination to give the more stable enol. Subsequent toutomerization of enol provides β-heteroaryl carbonyl compound.

Experimental Section

The infrared spectra were obtained on a Shimadzu IR-435 spectrometer, and ^1H and ^{13}C NMR spectra were obtained on a Varian Gemini, 200 MHz NMR Spectrometer. The GC-MS spectra were obtained on a Shimazu QP 1000 mass spectrometer. All chemicals were used directly as obtained from commercial sources or simple modification of commercially available compounds following literature procedures (2-cyano-3-bromopyridine,[16] 2-cyano-4-bromopyridine,[16] 5-iodo-2-methoxypyridine,[17] and 2-fluoro-5-iodopyridine[17]).

General procedure for the palladium-catalyzed heteroarylation of allylic alcohols. To a 10 mL vial containing a magnetic stirring bar was added the following reagents; $Pd(OAc)_2$ (0.025 mmol), appropriate base (1.0 mmol), LiCl (0.5 mmol), allylic alcohol (1.0 mmol), heteroaryl halide (0.5 mmol) and DMF (5 mL). The vial was sealed with a septum. The mixture was stirred at the desired temperature for 3-4 hours. The resulting reaction mixture was diluted with ethyl acetate (20 mL) and washed with saturated aqueous NH_4Cl (2×20 mL). The ethyl acetate layer was dried over anhydrous $MgSO_4$. The product was obtained by filtration, concentration, and purification *via* flash column chromatography.

The following compounds (**1a-9a**) were obtained using the above general procedure.

4-(3-Pyridyl)-2-butanone (1a)[10]. Yellow oil; yield 75%; IR (neat) 2927, 1714, 1423, 1367, 714 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.30 (s, 3H, $COCH_3$), 2.75-3.95 (m, 4H, CH_2), 7.40 (m, 2H, ArH), 7.50 (d, 1H, J = 7.9 Hz, ArH), 8.45 (s, 1H, ArH); Mass m/e (%) 41 (14), 43 (27), 51 (54), 65 (29), 78 (57), 92 (100), 109 (99), 121 (28), 153 (2, M^+).

3-(3-Pyridyl)propanal (1b)[10]. Yellow oil; yield 52%; IR (neat) 2930, 1690, 1368, 715 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.75-2.95 (m, 4H, CH_2), 7.40 (m, 2H, ArH), 7.50 (d, 1H, J = 7.9 Hz, ArH), 8.45 (s, 1H, ArH), 9.80 (s, 1H, CHO); Mass m/e (%) 43 (27), 51 (54), 65 (29), 78 (57), 92 (35), 109 (100), 139 (8, M^+).

3-(3-Oxobutyl)-2-pyridinecarbonitrile (2a). Yellow oil; yield 60%; IR (neat) 2954, 1724, 1432, 1295, 1165, 814 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.17 (s, 3H, $COCH_3$), 2.90-3.10 (m, 4H, CH_2), 7.60-7.80 (m, 2H, ArH), 8.40 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.3, 29.6, 42.9, 116.1, 126.7, 133.4, 137.8, 141.6, 148.7, 150.9, 206.0; Mass m/e (%) 41 (25), 51 (19), 65 (31), 91 (35), 119 (100), 146 (84), 178 (12, M^+).

Methyl 5-(3-propanal) nicotinate (3a)[18]. Yellow oil; yield 45%; IR (neat) 2954, 1724, 1432, 1295, 1114, 1027, 764, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.85-2.96 (m, 4H, CH_2), 3.90 (s, 3H, OCH_3), 8.12 (s, 1H, ArH), 8.63 (s, 1H, ArH), 9.03 (s, 1H, ArH), 9.80 (s, 1H, CHO); Mass m/e (%) 50 (55), 63 (49), 77 (100), 103 (24), 120 (43), 132 (45), 160 (67), 193 (27, M^+).

4-(6-Methoxy-3-pyridyl)-2-butanone (4a). Yellow oil;

yield 63%; IR (neat) 2950, 1716, 1592, 1465, 1411, 1254, 1021, 789 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.10 (s, 3H, $COCH_3$), 2.70-2.90 (m, 4H, CH_2), 3.95 (s, 3H, OCH_3), 6.70 (d, 1H, J = 8.5 Hz, ArH), 7.39 (d, 1H, J = 8.5 Hz, ArH), 8.97 (s, 1H, J = 8.5 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.7, 28.2, 51.5, 115.0, 121.7, 136.3, 142.8, 160.3, 206.2; Mass m/e (%) 45 (30), 73 (13), 95 (53), 109 (100), 149 (17), 180 (7, M^+).

4-(6-Fluoro-3-pyridyl)-2-butanone (5a). Yellow oil; yield 54%; IR (neat) 2927, 1710, 1420, 1367, 714 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.20 (s, 3H, $COCH_3$), 2.75-3.00 (m, 4H, CH_2), 7.15 (m, 1H, ArH), 7.70 (m, 1H, ArH), 8.10 (d, 2H, J = 8.5 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.8, 29.1, 45.4, 110.1, 137.6, 141.2, 147.9, 161.5, 207.1; Mass m/e (%) 51 (11), 65 (12), 91 (18), 108 (100), 121 (31), 167 (49, M^+).

4-(3-Oxobutyl)-2-pyridinecarbonitrile (6a). Yellow oil; yield 60%; IR (neat) 2947, 2230, 1708, 1565, 1426, 1165, 814 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.17 (s, 3H, $COCH_3$), 2.80-3.00 (m, 4H, CH_2), 7.30 (d, 1H, J = 5.6 Hz, ArH), 7.57 (s, 1H, ArH), 8.57 (d, 1H, J = 5.6 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.3, 28.6, 45.2, 118.1, 126.7, 128.3, 133.8, 151.1, 207.1; Mass m/e (%) 41 (25), 51 (8), 65 (27), 91 (35), 119 (100), 146 (84), 178 (5, M^+).

4-(1-Benzyl-1*H*-4-pyrazolyl)-2-butanone (7a). Yellow oil; yield 72%; IR (neat) 2929, 1712, 1455, 1359, 1163, 995, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.20 (s, 3H, $COCH_3$), 2.75-3.00 (m, 4H, CH_2), 5.30 (s, 2H, CH_2Ph), 7.20-7.40 (m, 6H, ArH), 7.50 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.4, 28.4, 42.6, 54.0, 119.8, 126.5, 126.9, 127.4, 128.0, 133.4, 134.9, 149.3, 206.0; Mass m/e (%) 53 (79), 65 (13), 77 (21), 109 (100), 134 (9), 172 (4), 228 (15, M^+).

4-[4-(2-Benzyl)-2*H*-1,2,3,4-tetarzol-5-yl)phenyl]-2-butanone (8a). Yellow oil; yield 65%; IR (neat) 2955, 2921, 1706, 1464, 1040, 831, 719 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.15 (s, 3H, $COCH_3$), 2.70 (m, 4H, CH_2), 5.25 (s, 2H, CH_2), 7.10-7.30 (m, 9H, ArH); ^{13}C NMR ($CDCl_3$) δ 27.9, 28.5, 43.1, 55.0, 123.7, 125.4, 126.7, 127.1, 127.2, 127.3, 131.7, 141.9, 149.3, 163.7, 205.9; Mass m/e (%) 43 (100), 57 (9), 73 (10), 84 (71), 103 (8), 130 (17), 175 (20), 201 (36), 260 (2), 306 (3, M^+).

Methyl 4-(3-oxobutyl)-2-furoate (9a). Yellow oil; yield 61%; IR (neat) 2360, 2348, 1737, 1649, 1530, 1390, 1171 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.10 (s, 3H, $COCH_3$), 2.70-2.90 (m, 4H, CH_2), 3.95 (s, 3H, OCH_3), 7.10 (s, 1H, ArH), 7.40 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.1, 28.2, 39.4, 50.1, 106.5, 117,5, 141.5, 157.4; 157.8, 204.7; Mass m/e (%) 59 (15), 80 (45), 125 (100), 137 (45), 187 (12), 196 (8, M^+).

Conclusions

Our established LiCl-mediated heteroarylation of allylic alcohol is a very convenient and practical method for the preparation of β-heteroaryl carbonyl compounds, which could not be easily synthesized by conventional methods. The process can also be attractive in view of simplicity, high regioselectivity, and availablity of various heteroaromatics.

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