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Synthesis of 4-carboxy-4-pyridylpiperidines through palladium-catalyzed α-arylation of esters

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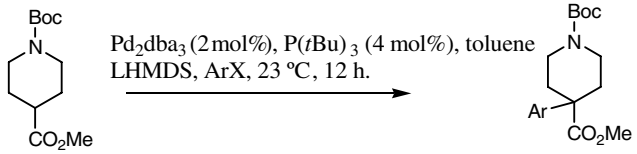
Abstract—A concise synthesis of 4-carboxy-4-pyridylpiperidines has been achieved. Key step is the palladium-catalyzed α-arylation of esters under basic conditions.

4-Arylpiperidines are important building blocks found in several important pharmaceuticals. Examples include the analgesic Trefentanil (**1**),[1] Pethidine (**2**),[2] and the antidiarrheal Loperamide (**3**) (Fig. 1).[3] Thus, synthesis of these building blocks is of intense interest in discovery chemistry.

In our small molecule drug discovery efforts we targeted the synthesis of 4-carboxy-4-pyridylpiperidines as building blocks. 4-Carboxy-4-pyridylpiperidine derivatives has been prepared by condensation of 2-pyridylacetonitirle with di-(2-chloroethyl)-methylamines.[4] However, few pyridylacetonitriles are commercially available. As a result, parallel synthesis is severely limited. Hence we sought to develop a general new protocol to allow us to carry parallel medicinal chemistry. Herein we reported the synthesis of 4-carboxy-4-pyridylpiperidine analogues through palladium-catalyzed α-arylation of esters.



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Scheme 1.

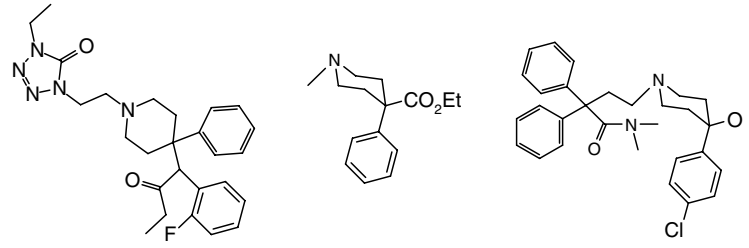

Figure 1.

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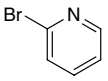
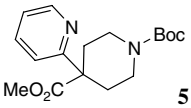
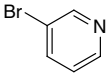
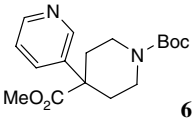
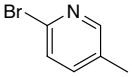
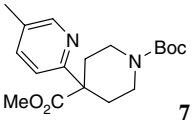
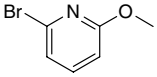
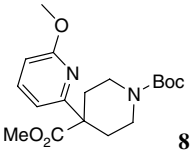
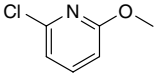
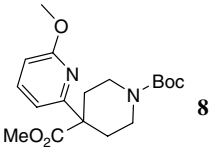
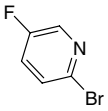
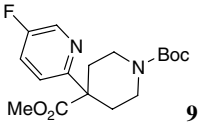
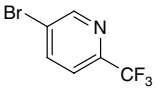
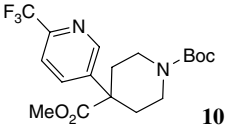
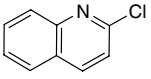
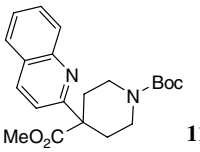
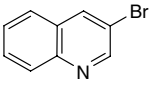
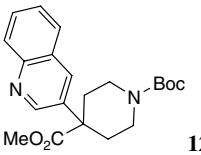
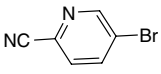
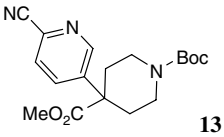
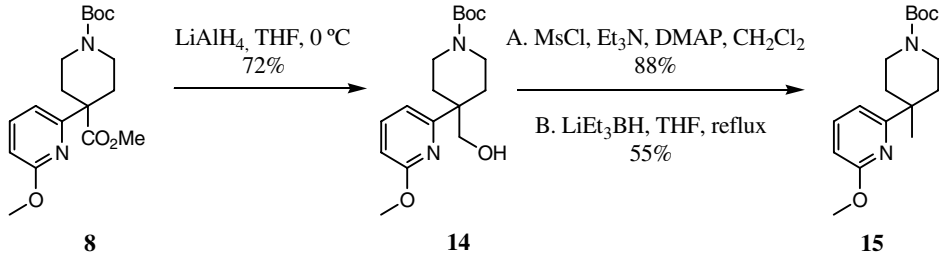
Table 1. Palladium-catalyzed α-arylation of esters[a]

Entry	ArX	Product	Isolated yield
1		 **5**	91
2		 **6**	46
3		 **7**	95
4		 **8**	94
5		 **8**	93
6		 **9**	93
7		 **10**	72
8		 **11**	86
9		 **12**	92
10		 **13**	0

[a] Reactions were conducted for 12 h at room temperature using 1 equiv of halide and 2 equiv of ester and 2.2 equiv of LHMDS, 2 mol % Pd_2dba_3 and 4 mol % P(*t*-Bu)$_3$ in toluene.

Hartwig[5] and Buchwald[6] have recently described their α-arylation of esters. However, application of this versatile palladium-catalyzed reaction to heterocyclic arrays of pharmaceutical interest is quite limited. Thus, arylation of *N*-Boc-4-methoxycarbonylpiperidine (**4**) with a series of chloropyridine and bromopyridine, LHMDS, and a catalytical amount of Pd_2dba_3 and P(*t*-Bu)$_3$ was carried out (Scheme 1). The results are summarized in Table 1.[7]



8 **14** **15**

Scheme 2.

The reactions of ester **4** with unsubstituted pyridyl bromides went smoothly at room temperature in moderate to excellent yield (entries 1 and 2). Pyridyl halides with electron-donating groups gave excellent yields and short reaction times (entries 3–5). Chloropyridine works equally well as bromopyridine (entries 4 and 5). Halides with electron-withdrawing groups also gave good yields (entries 6 and 7). No byproduct from the competing nucleophilic attack on the pyridyl halide was observed. However, for halides bearing cyano groups, no product **13** was observed due to the nucleophilic attack on the cyano group to form amidine (entry 10). The reactions of ester **4** with bicyclic quinolyl halide also gave an excellent yield (entries 8 and 9). Attempts to change reaction conditions to improve the yield (for example, use *tert*-butyl ester instead of methyl ester and replacing LHMDS with NaHMDS) were not successful.

4-Carboxy-4-pyridylpiperidine is an important intermediate in the synthesis of other biologically active pharmaceuticals. The ester group can be transformed to other functional groups such as amide, alcohol, methyl or other heterocyclic groups. Scheme 2 illustrates the example of transformation to the methyl group. 4-Methyl-4-phenylpiperidine has been made by Friedel–Crafts arylation of the tertiary alcohol in the presence of substituted benzene and aluminum trichloride.[8] However, this protocol is not amenable for electron-deficient systems such as pyridine. This transformation was achieved in a three-step sequence.[9] First, reduction of the ester with lithium aluminum hydride to give primary alcohol **14** in a 72% yield. Second, treatment of the alcohol with methanesulfonyl chloride in the presence of Et_3N and 5% DMAP furnished the mesylate in an 88% yield; finally, reduction of mesylate to the corresponding methyl group was achieved with super-hydride in reflux for 12 h to furnish the desired product **15** in a 55% yield.[10] Direct deoxygentation of alcohol through $B(C_6F_5)_3$ and triethylsilane was not successful.[11]

In conclusion, we have developed a protocol for synthesizing 4-carboxy-4-pyridylpiperidines. The key step is the palladium-catalyzed arylation of ester under basic conditions. This method should be of application to the synthesis of other 4-carboxy-4-heteroarylpiperidine intermediates (such as pyrimidine, oxazole, imidazole), which will be reported in due course. Further modification to expand the scope of this protocol by carrying out palladium-catalyzed α-arylation under neutral conditions is underway.

References and notes

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7. Representative procedure, 1-*tert*-butyl 4-methyl 4-(6-methylpyridin-2-yl)piperidine-1,4-dicarboxylate (**7**): To a solution of 1-*tert*-butyl 4-methyl piperidine-1,4-dicarboxylate (**4**) (430 mg, 1.77 mmol), 2-bromo-5-methylpyridine (152 mg, 0.88 mmol), Pd_2dba_3 (32 mg, 0.035 mmol), P-(*t*-Bu)$_3$ (0.070 mL, 0.07 mmol; 1.0 M in toluene) in toluene (5 mL) was added LHMDS (1.9 mL, 1.9 mmol; 1.0 M in toluene) dropwise at room temperature. The solution turned from dark red to dark brown. After 24 h, the mixture was quenched with saturated aqueous ammonium chloride. The mixture was partitioned between EtOAc and water. The combined organic extracts were dried over sodium sulfate and concentrated to give a residue, which was purified by silica gel chromatography (10% EtOAc/hexanes) to give the product as a colorless oil (280 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.45 (s, 9H), 1.98–2.11 (m, 2H), 2.31 (s, 3H), 2.33–2.37 (m, 2H), 3.03–3.11 (m, 2H), 3.62 (s, 3H), 3.77–3.80 (m, 2H), 7.21 (d, $J = 8.08$ Hz, 1H), 7.48 (dd, $J = 8.08$, 2.27 Hz, 1H), 8.40 (d, $J = 1.52$ Hz, 1H). LC–MS (EI) *m*/*z* 335.1 [M+H].
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9. (a) Zhao, D.; Kuethe, J. T.; Journet, M.; Peng, Z.; Humphery, G. R. *J. Org. Chem.* **2006**, *71*, 4336; (b) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064.
10. All compounds were characterized via NMR (Bruker AM 400) and LC/MS. *tert*-Butyl 4-(hydroxymethyl)-4-(6-methoxypyridin-2-yl)piperidine-1-carboxylate (**14**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 9H), 1.87–2.01 (m, 2H), 2.21–2.34 (m, 2H), 3.28–3.37 (m, 2H), 3.51–3.55 (m, 2H), 3.76 (s, 2H), 3.85 (s, 3H); 4.11 (s, 1H), 6.47 (d, $J = 8.34$ Hz, 1H), 6.70 (d, $J = 7.58$ Hz, 1H), 7.39 (t, $J = 7.83$ Hz, 1H). LC–MS (EI) *m*/*z* 323.1 [M+H]. *tert*-Butyl 4-(6-methoxypyridin-2-yl)-4-methylpiperidine-1-carboxylate (**15**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.44 (s, 9H), 1.57–1.70 (m, 2H), 2.20–2.36 (m, 2H), 3.15–3.30 (m, 2H), 3.59 (br s, 2H), 3.90 (s, 3H), 6.55 (d, $J = 8.34$ Hz, 1H), 6.83 (d, $J = 7.58$ Hz, 1H), 7.52 (t, $J = 7.83$ Hz, 1H). LC–MS (EI) *m*/*z* 307.1 [M+H].
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