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Palladium-catalyzed *N*-arylation of *O*-methylamidoximes

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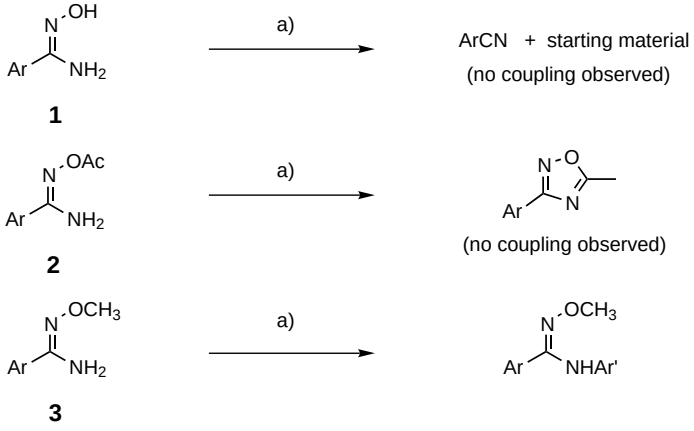
Abstract—Pd-catalyzed coupling of *O*-methylbenzamidoximes gave *N*-aryl *O*-methylbenzamidoximes using aryl halides with electron attracting or moderate electron donating groups. Under the same conditions, benzamidoxime failed to undergo coupling and *O*-acetylbenzamidoxime underwent cyclization to form the corresponding [1,2,4]oxadiazole. © 2002 Published by Elsevier Science Ltd.

Amidoximes are synthetically useful precursors for various heterocyclic systems[1] and the key intermediate for an important route for amidine synthesis.[2] Furthermore, amidoxime-containing molecules have found a number of significant uses in the polymer field[1a,3] and as potential drugs in a wide range of therapeutic areas.[1a] This functional group can also serve as a prodrug unit for amidines.[4] Structurally diverse *N*-unsubstituted amidoximes can be readily synthesized by the reaction of hydroxylamine with either aliphatic or aromatic nitriles.[5] The synthesis of *N*-substituted amidoximes is much less straightforward, however, involving intermediates that require multi-step synthesis and, in some cases, are water sensitive. For example, *N*-phenylbenzamidoxime has been prepared by the action of hydroxylamine on *N*-phenylthiobenzamide,[6] *N*-phenylbenzamidine,[7] or *N*-phenylbenzimidoyl chloride,[8] and by the reaction of *N*-hydroxybenzimidoyl chloride[9] or benzonitrile oxide with aniline.[10]

Several recent reports have described the palladium-catalyzed formation of new nitrogen–carbon bonds by the coupling of aryl halides with various nitrogen-containing systems.[11] For example, the syntheses of aryl substituted amines,[12] lactams,[13] amides,[14] oxazolidones,[15] carbamates,[12b] ureas[16] and hydrazides[17] by Pd-catalyzed chemistry have appeared. Pd-catalyzed carbonylation of amidoximes to give oxadiazoles has been described,[18] however, there is no report of the *N*-arylation of amidoximes. In this report we describe, for the first time, the Pd-catalyzed *N*-arylation chemistry of amidoximes with aryl halides.



Scheme 1. *Reagents and conditions*: Ar′Br, $Pd_2(dba)_3$, Xantphos, Cs_2CO_3, dioxane, 100°C.

Keywords: coupling reactions; Pd-catalyst; aryl halides; *N*-aryl *O*-methylbenzamidoximes.

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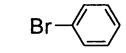
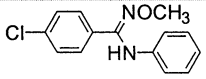
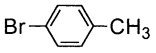
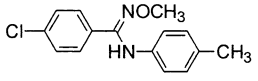
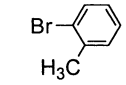
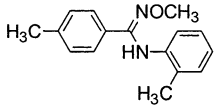
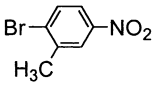
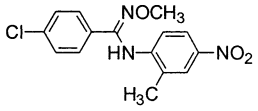
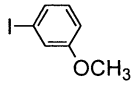
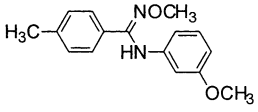
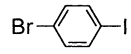
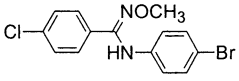
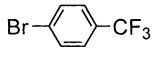
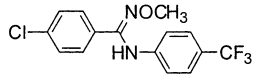
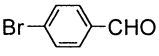
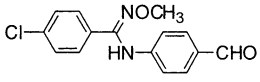
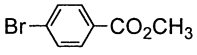
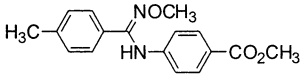
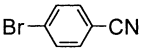
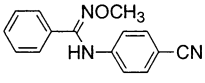
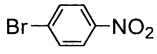
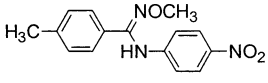
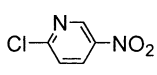
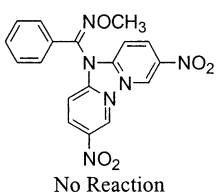
Initially, we allowed 4-methylbenzamidoxime (**1**) to react with 4-bromobenzonitrile in the presence of $Pd_2(dba)_3$, Xantphos and Cs_2CO_3 in dioxane at 100°C, conditions that were developed by Yin and Buchwald for the *N*-arylation of amides.[14] After 48 h, the starting amidoxime was substantially recovered, with a small amount of *p*-tolunitrile detected by NMR (ca. 15%).[19] In contrast, the Pd-assisted carbonylation of amidoximes has been reported to proceed under similar conditions.[18] Due to the low reactivity of the amidoxime, we decided to protect the hydroxyl group by acetylation. *O*-Acetyl 4-methylbenzamidoxime (**2**) was thus prepared[2a] and subjected to the above coupling conditions. In this case, cyclization of the acetyl unit to form the corresponding oxadiazole was observed, again with no evidence of *N*-arylation. The facile cyclization of acetoxyamidoximes to oxadiazoles has been well studied.[20]

In view of the above results, we decided to protect the hydroxyl group by alkylation and examined the chemistry of *O*-methylbenzamidoximes. In contrast to the successful reaction of hydroxylamine with *p*-tolunitrile to give **1**, *O*-methylhydroxylamine failed to react with *p*-tolunitrile under comparable conditions. There is a suggestion in the literature that activated nitriles are

Table 1. Pd-catalyzed *N*-arylation of *O*-methylamidoximes with aryl halides

Entry	Aryl halide	Mol % Pd/ligand	Reaction time, h	Product	% Yield[a]
1		2	18		72[b]
2		2	20		61
		3	20		79
3		3	48		26
4		2	14		64
5		2	48		78
6		3	36		79
7		3	14		84
8		2	15		69
9		1	24		84
10		2	20		87
11		2	14		72
12		2	20		81[c]
		0	20		0
13	2-Bromothiophene	3	48	No Reaction	
14	2-Bromopyridine	3	48	No Reaction	
15	4-Bromoanisole	3	48	No Reaction	
16	4-Iodoanisole	3	48	No Reaction	

[a]Reported yields represent analytically pure material. [b]Iodobenzene gave the same product in 81% yield. [c]Yield based on the aryl halide.

required for reaction with *O*-methylhydroxylamine.[21] Consequently, it was necessary to prepare the *O*-methylbenzamidoximes **3** by an indirect approach, which involved the *O*-methylation of **1** using methylsulfate.[22]

Palladium-catalyzed coupling of the *O*-methylbenzamidoximes proceeded smoothly using $Pd_2(dba)_3$, Xantphos and Cs_2CO_3 in dioxane to give the desired *N*-aryl *O*-methylbenzamidoximes (Scheme 1). Preliminary studies of the effect of catalyst, ligand and base on the course of the reaction were performed using *O*-methyl-4-chlorobenzamidoxime and 4-bromotoluene. The coupling reaction failed to proceed when $Pd_2(dba)_3$/BINAP or $Pd(OAc)_2$/Xantphos were used as catalyst/ligand, and also when K_2CO_3 was used as base in place of Cs_2CO_3. The scope and limitations of the reaction was thus further explored using the initial coupling conditions.

As shown in Table 1, the coupling with *para*- and *meta*-substituted aryl halides containing various electron attracting groups or moderate electron donating groups proceeded to give isolated yields ranging from 61 to 87%.[23,24] Coupling with an *ortho*-substituted halide gave a significantly lower isolated yield (26%, entry 3), however, this was much improved with an activated substrate (64%, entry 4). A catalyst/ligand loading of 2–3 mol% was generally required for sufficient reactivity with most examples, although in one case, 1 mol% gave high yield with an activated halide (entry 9). Coupling with 2-bromothiophene (entry 13) and 2-bromopyridine (entry 14) failed under our standard conditions, with the latter also failing to couple with a CuI catalyst system[25] that has been used with nitrogen heterocycles. In contrast, coupling with the highly electron deficient 5-nitro-2-chloropyridine led to diarylation of nitrogen in an 81% yield based on aryl halide (entry 12). Finally, with 4-bromo- and 4-iodoanisole (entries 15 and 16), no isolable amount of coupling product was observed, which is consistent with the diminished reactivity found with this catalyst system in the *N*-arylation of amides[14] and ureas[16] with electron rich halides.

In conclusion, we have described a straightforward method for the synthesis of *N*-aryl *O*-methylbenzamidoximes employing the Pd-catalyzed coupling of *O*-methylbenzamidoximes and aryl halides. Under these conditions, both benzamidoxime and *O*-acetyl benzamidoxime failed to undergo *N*-arylation and formed other products.

Acknowledgements

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23. Typical example: An oven-dried round-bottomed flask was charged with $Pd_2(dba)_3$ (18.3 mg, 0.02 mmol, 2 mol%), Xantphos (11.6 mg, 0.02 mmol, 2 mol%), Cs_2CO_3 (456 mg, 1.4 mmol), iodobenzene (0.137 mL, 249 mg, 1.2 mmol), *O*-methyl-*p*-chlorobenzamidoxime (174 mg, 1.0 mmol) and anhydrous dioxane (4 mL). This mixture was stirred at 100°C for 18 h under nitrogen. TLC showed the complete consumption of starting amidoxime. The mixture was diluted with water, extracted with ethyl acetate, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, ethyl acetate–hexane, 1:20) to afford *O*-methyl-*N*-phenyl-*p*-chlorobenzamidoxime as a pale yellow oil in 81% yield. δ ^{1}H NMR ($CDCl_3$): 3.83 (s, 3H, OMe); 6.66 (d, 2H, $J=5.0$ Hz, Ar); 6.81 (m, 1H, Ar); 7.08 (d, 2H, $J=5.0$ Hz, Ar); 7.36 (m, 4H, Ar); 8.78 (br, 1H, NH). δ ^{13}C NMR ($CDCl_3$): 61.6, 121.2, 122.7, 128.5, 128.6, 128.8, 129.5, 135.4, 139.4, 145.0. MS (EI) m/z (%): 260.1 (56), 229.1 (100), 214.1 (44), 180.1 (6), 153 (35), 137 (43), 92 (43), 77 (59). Anal. calcd for $C_{14}H_{14}N_2OCl_2$ (HCl salt): C, 56.75; H, 4.72; N, 9.45. Found: C, 57.03; H, 4.91; N, 9.32%.
24. All products were characterized by NMR (^{1}H, ^{13}C) and MS.
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