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Synthesis of Tertiary Benzamides via Pd-Catalyzed Coupling of Arylboronic Esters and Carbamoyl Chlorides

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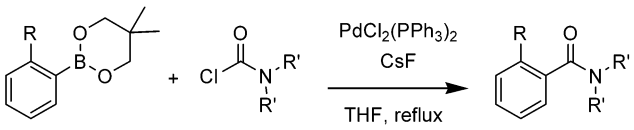
Received March 9, 2005



Ortho-substituted arylboronic esters are efficiently coupled with carbamoyl chlorides under Pd-catalysis to give tertiary benzamides.

The benzamides are a very important class of compounds with a wide range of applications. They are usually prepared via the addition of an amine to an activated benzoic acid derivative, e.g., an acid chloride (route A in Figure 1). An alternative and much less used approach to benzamides is the addition of a metalated-benzene derivative to a carbamoyl chloride (route B in Figure 1).

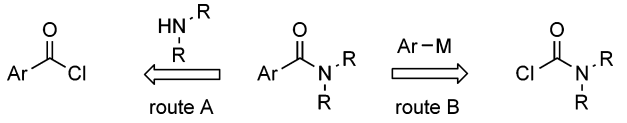
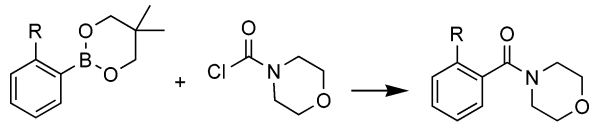


FIGURE 1. Different synthetic routes to benzamides.

Lemoucheux et al. reported the synthesis of tertiary amides via Ni-catalyzed addition of Grignard reagents to carbamoyl chlorides and the direct addition of organocuprates to carbomoyl chlorides.[1] Earlier reports describe the Pd-catalyzed coupling of carbamoyl chlorides with stannanes.[2] The Pd-catalyzed coupling of arylboronic derivatives with organohalides, the Suzuki−Miyaura coupling,[3] has become widespread for the construction of C−C bonds. We were intrigued by the prospect of preparing benzamides via the coupling of arylboronic derivatives with carbamoyl chlorides and set out to explore this possibility.[4]

TABLE 1. Coupling of Arylboronic Esters with 4-Morpholinecarbonyl Chloride[a]



1a-g 2 3a-g

entry	boronic ester	R	product	isolated yield (%)
1	**1a**	H	**3a**	79
2	**1b**	F	**3b**	87
3	**1c**	Cl	**3c**	94
4	**1d**	CN	**3d**	87
5	**1e**	Ph	**3e**	76
6	**1f**	OMe	**3f**	86
7	**1g**	NHBoc	**3g**	79

[a] Reaction conditions: arylboronic ester (2 mmol), 4-morpholinecarbonyl chloride (4 mmol), CsF (4 mmol), $PdCl_2(PPh_3)_2$ (0.06 mmol) in THF (8 mL), reflux 16 h.

We chose to examine the coupling of neopentylglycol arylboronic esters instead of free arylboronic acids, as this makes it possible to monitor the progress of the reactions via GC−MS.[5] A series of ortho-substituted arylboronic esters (**1a**−**g**, Table 1) with different electronic and steric properties were selected.[6] As carbamoyl chloride coupling partner we chose 4-morpholinecarbonyl chloride (**2**) as the resulting amides (**3a**−**g**) serve as cheap alternatives to Weinreb amides,[7] making them very useful intermediates for further transformation.

Testing different bases, Pd catalysts, and solvents revealed that the use of CsF[8] as base in combination with $PdCl_2(PPh_3)_2$ in THF or dioxane did indeed induce the coupling to give the desired amides, and we settled on the following conditions: 2 equiv of carbamoyl chloride, 2 equiv of CsF, 3% $PdCl_2(PPh_3)_2$ in THF at reflux. Excess of the carbamoyl chloride is nesccessary as it is slowly converted to the corresponding carbamoyl fluoride during the course of the reaction. As seen in Table 1, the coupling of a series of ortho-substituted neopentylglycol arylboronic esters with **2** gave the desired morpholinamides in good to excellent yield.

(1) (a) Lemoucheux, L.; Rouden, J.; Lasne, M.-C. *Tetrahedron Lett.* **2000**, *41*, 9997. (b) Lemoucheux, L.; Seitz, T.; Rouden, J.; Lasne, M.-C. *Org. Lett.* **2004**, *6*, 3703.

(2) (a) Balas, L.; Jousseaume, B.; Shin, H.; Verlhac, J.-B.; Wallian, F. *Organometallics* **1991**, *10*, 366. (b) Jousseaume, B.; Kwon, H.; Verlhac, J.-B.; Denat, F.; Dubac, J. *Synlett* **1993**, 117. (c) Murakami, M.; Hoshino, Y.; Ito, H.; Ito, Y. *Chem. Lett.* **1998**, 163.

(3) Miyaura, M.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(4) During the preparation of this manuscript, a paper appeared describing the coupling of para-substituted arylboronic acids with *N*,*N*-dibutyl chloroformate; see: Duan, Y.-Z.; Deng, M.-Z. *Synlett* **2005**, 355.

(5) Neopentylglycol arylboronic esters can be prepared very conveniently from the parent arylboronic acids in the following way: Equimolar amounts of arylboronic acid and neopentylglycol are stirred in CH_2Cl_2 (3−5 mL/mmol) at rt. Initially, the mixture is heterogeneous as arylboronic acids are generally not very soluble in CH_2Cl_2. After approximately 1 h, the mixture becomes clear, indicating that the reaction is complete. The CH_2Cl_2 phase is washed with water and brine, dried over Na_2SO_4, filtered, and the solvent is removed, leaving the neopentylglycol arylboronic esters. See also: Kristensen, J. L.; Lysén, M.; Vedsø, P.; Begtrup, M. *Org. Synth.* **2005**, *81*, 134.

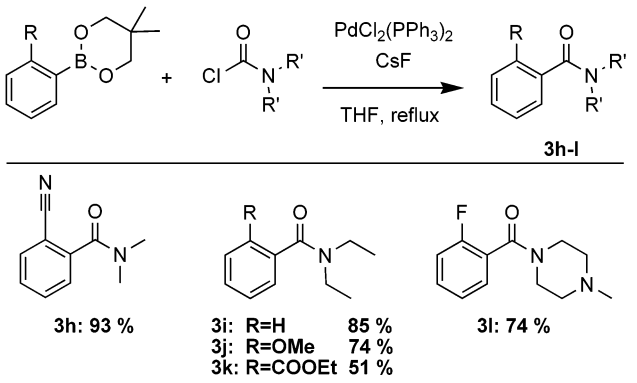
(6) **1a**: Bowie, R. A.; Musgrave, O. C.; *J. Chem. Soc. C* **1963**, 3945. **1b**−**d**: Kristensen, J.; Lysén, M.; Vedsø, P.; Begtrup, M. *Org. Lett.* **2001**, *3*, 1435. **1e**: Bowie, R. A.; Musgrave , O. C. *J. Chem. Soc. C*, **1966**, 566. **1f**: Chaumeil, H.; Signorella, S.; Le Drian, C. *Tetrahedron* **2000**, *56*, 9655. **1g**: Eskildsen, J.; Østergaard, N.; Vedsø, P.; Begtrup, M. *Tetrahedron* **2002**, *58*, 7635.

(7) Jackson, M. M.; Leverett, C.; Toczko, J. F.; Roberts, J. C. *J. Org. Chem.* **2002**, *67*, 5032 and references therein.

(8) K_2CO_3, Na_2CO_3, K_3PO_4, NaF, and KF all gave inferior results. Fluoride activation in Suzki couplings: (a) Ichikawa, J.; Moriya, T.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1991**, 961. (b) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095.

10.1021/jo050459h CCC: $30.25
Published on Web 05/21/2005

TABLE 2. Coupling of Arylboronic Esters with Other Carbamoyl Chlorides



To investigate the scope of the reaction with respect to the carbamoyl chlorides, a series of different carbamoyl chlorides were coupled with selected arylboronic esters. Simple alkyl carbamoyl chlorides as well as 4-methylpiperazine-1-carbonyl chloride performed equally well. As seen in Table 2, the desired amides **3h**−**l** were isolated in 51−93% yield using the conditions optimized for the coupling of arylboronic esters with **2**.

In conclusion, we have described the Pd-catalyzed coupling of arylboronic esters with carbamoyl chlorides to give tertiary benzamides. This represents a useful addition to the growing application of arylboronic esters in preparative organic chemistry.

Experimental Section

Representative Experimental Procedure for the Coupling of Arylboronic Esters with Carbamoyl Chlorides. 2-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)benzonitrile (**1d**) (430 mg, 2.00 mmol), CsF (608 mg, 4.0 mmol), $PdCl_2(PPh_3)_2$ (42.0 mg, 0.06 mmol), and 4-morpholinecarbonyl chloride (460 μL, 4.00 mmol) were dissolved in THF (8 mL) under N_2. The mixture was heated at 80 °C for 16 h. At rt, the mixture was evaporated onto Celite and purified by FC giving 377 mg (87%) 2-(morpholine-4-carbonyl)benzonitrile (**3d**) as an off-white solid: mp (EtOAc/PE) 107−109 °C.

Supporting Information Available: Full characterization of **3d**, **3e**, and **3g** as well as references to known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050459H