ORGANIC LETTERS

2009
Vol. 11, No. 8
1677−1680

Selective Monomethylation of Anilines by $Cu(OAc)_2$-Promoted Cross-Coupling with $MeB(OH)_2$

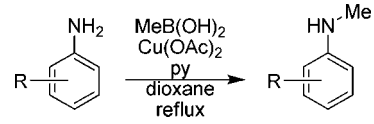
Israel González, Jesús Mosquera, César Guerrero, Ramón Rodríguez, and Jacobo Cruces*

GalChimia, S.L. R&D Department, Cebreiro s/n 15823 O Pino, A Coruña, Spain

jacobo.cruces@galchimia.com

Received January 19, 2009

ABSTRACT



***N*-Methylanilines are readily synthesized in high yields through the copper(II)-promoted coupling of anilines and methylboronic acid. This method represents a new approach for the selective monomethylation of anilines, and it is the first reported example of a Chan-Lam coupling involving the use of methylboronic acid. An incubation period of the substrate with the copper reagent is needed before addition of the methylboronic acid.**

Anilines are important compounds found throughout the pharmaceutical and agrochemical industries.[1] In the last few years, C−N bond forming reactions have become one of the most explored reactions, especially regarding *N*-arylation.[2] Although selective monoarylation of anilines can be easily achieved, aniline monoalkylation (particularly *N*-methylation) represents a challenging task which has been barely investigated despite the prevalence of the methylamino moiety in drug candidates.[3] Classical approaches call for the use of a base and an alkylating agent, or reductive amination with formaldehyde. Although both methods are widely described in the literature, they lack from selectivity (mono and dimethylated compounds are usually obtained) and require a carefully controlled addition of reagents. Besides that, there are problems associated with the toxicity of the methylating reagents and functional group tolerance for reductive aminations.

Two alternative methods have been developed to overcome these problems. The first is the functionalization based on the use of a temporary protecting group (e.g., carbamate, benzyl) that allows the introduction of the methyl moiety, followed by removal of the protecting group. The second method for the monomethylation of a primary aniline is the full reduction of a carbamate with LAH or other reducing agent. Both methods involve the use of a protecting group or the use of a powerful reducing reagent, so several steps are introduced or harsh reaction conditions must be used.

Copper-promoted carbon−nitrogen bond forming cross-coupling reactions of NH-containing substrates with arylboronic acids have emerged as a powerful synthetic method

(1) (a) Negwer, M. *Organic-Chemical Drugs and their Synonyms: (An International Survey)*, 7th ed.; Akademie Verlag GmbH: Berlin, 1994. (b) Montgomery, J. H. *Agrochemicals Desk Reference: Environmental Data*; Lewis Publishers: Chelsea, MI, 1993.

(2) (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2047–2067. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852–860. (c) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901–7902. (d) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818. (e) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413–2416. (f) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157. (g) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793–796.

(3) As an example, a search in the Integrity database showed 1340 biologically active compounds with the dimethylaminoaryl moiety and 250 compounds with the methylaminoaryl moiety. These numbers do not include methyl- or dimethylaminoheteroaryl moieties.

(4) (a) Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933–2936. (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941–2944. (c) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, 674–676. (d) Lam, P. Y. S.; Deudon, S.; Kristin, M. A.; Li, R.; He, M.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *22*, 7600–7601.

10.1021/ol802882k CCC: $40.75
Published on Web 03/20/2009

since the initial reports by Chan and Lam.[4] Nitrogen-based nucleophiles are usually arylated at room temperature using a stoichiometric amount of a copper salt and several equivalents of a base.

Many extensions and applications of this new method have been reported, including the catalytic version of the reaction,[5] arylation of amines under base and ligand-free conditions,[6] tandem cross-coupling reactions,[7] and solid-phase chemistry.[8]

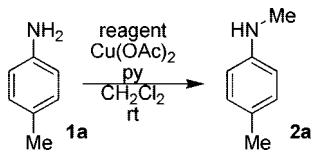
The reaction has been applied to a plethora of boronic acids, including aryl, vinyl, and heteroaryl compounds, but to the best of our knowledge, among the alkylboronic acids only cyclopropyl- and cyclohexylboronic acid have been successfully employed in this coupling to date.[9] The amine substrates selected are indoles, azoles, amides, and sulfonamides, where the NH has increased acidity. Additionally, in many of these compounds, a dialkylation is not possible and if encountered no further studies to minimize this side reaction are carried out.

Recently the organotrifluoroborates have been used in this type of coupling, but only in the arylation of alcohols.[10] Once again, these reagents can be successfully used for the coupling of aryl or alkenyl counterparts, but not for alkyl introduction.

Although there were no examples of this kind of transformation, we decided to explore the use of the Chan-Lam reaction for the methylation of anilines.

First, we ran the reaction under "classical" Chan-Lam conditions, using three different methylboron sources (methylboronic acid, trimethylboroxine, and potassium methyltrifluoroborate): a mixture of pyridine, *p*-toluidine (**1a**), and methyl transferring reagent were allowed to react at room temperature in CH_2Cl_2. After 3 days the desired monomethylated product was formed in a 4% (entry 1, Table 1),

Table 1. Efficacy of the Boronic Reagent on the Coupling[a]



entry	reagent	time (days)	HPLC conversion (%)
1	$MeB(OH)_2$	3	4
2	$MeBF_3K$	5	not detected
3	$(MeOB)_3$	5	not detected

[a] Reaction conditions: 1 mmol of *p*-toluidine (**1a**), 2 mmol of methylboronic reagent, 1.7 mmol of $Cu(OAc)_2$ and 3.5 mmol of pyridine in CH_2Cl_2 were allowed to react at room temperature.

only when $MeB(OH)_2$ was used. These results showed that the cross-coupling was feasible, and prompted us to undertake a deeper study of the reaction.

Several copper(I) and copper(II) salts were evaluated for the desired transformation, finding that $Cu(OAc)_2$ was the best copper salt. Other copper sources gave lower conversions, and Pd chemistry totally failed to afford the product. Conversion was always very low, so we carried out a broad check of solvents and temperatures (Table 2). Reaction only

Table 2. Solvent and Base Influence[a]

entry	base	solvent	yield (%)[b]
1	pyridine	CH_2Cl_2	9
2	pyridine	$Cl_2CH_2CH_2Cl_2$	23
3	pyridine	THF	29
4	pyridine	xylenes	33
5	pyridine	DMF	24
6	pyridine	CH_3CN	37
7	pyridine	dioxane	53
8	DIPEA	dioxane	21
9	Et_3N	dioxane	42

[a] Reaction conditions: 1 mmol of *p*-toluidine (**1a**), 1.5 mmol of methylboronic acid, 1.7 mmol of $Cu(OAc)_2$ and 3.5 mmol of base in the solvent of choice were refluxed for 18 h. [b] Isolated yields.

takes place at a significant rate under reflux. The best results were obtained in refluxing dioxane (entry 7, Table 2). We also briefly explored the effect of changing the base from pyridine to Et_3N or DIPEA, confirming that pyridine was the base of choice for this transformation (entries 8−9, Table 2).

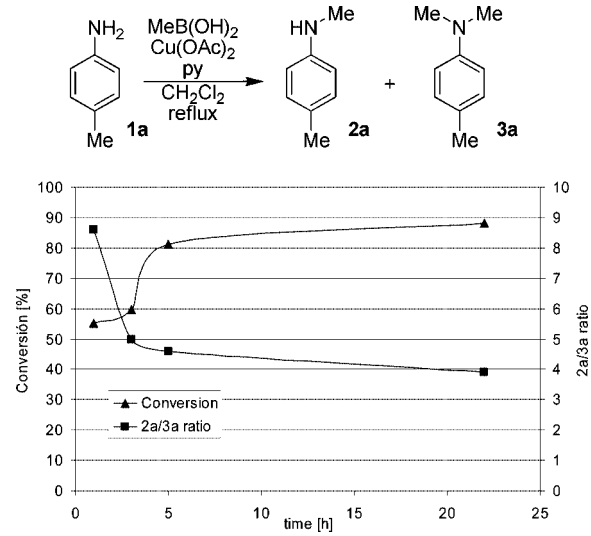


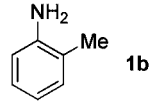
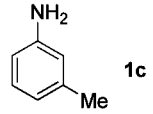
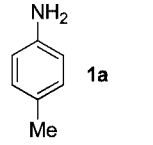
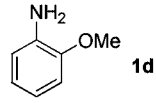
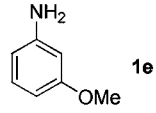
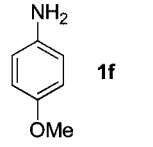
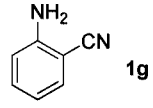
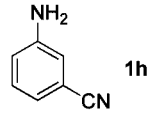
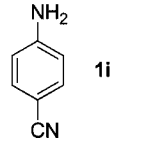
Figure 1. Conversion and monomethyl/dimethyl ratio for the copper promoted methylation of *p*-toluidine (**1a**, entry 7, Table 2).

To find the most efficient ratios between $Cu(OAc)_2$, pyridine and $MeB(OH)_2$ we applied Design of Experiments

(5) (a) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233–1236. (b) Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077–2079. (c) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415–3418.

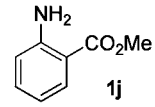
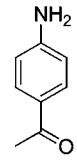
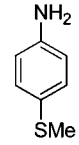
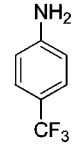
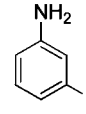
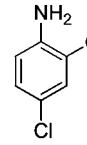
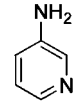
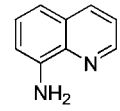
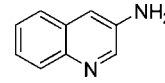
(6) (a) Moessner, C.; Bolm, C. *Org. Lett.* **2005**, *7*, 2667–2669. (b) Lan, J.-B.; Zhang, G.-L.; You, J.-S.; Chen, L.; Yan, M.; Xie, R.-G. *Synlett* **2004**, 1095. (c) Sreedhar, B.; Venkanna, G. T.; Kumar, K. B. S.; Balasubrahmanyam, V. *Synthesis* **2008**, 795–799.

Table 3. Copper-Promoted Monomethylation of Anilines[a]

entry	substrate	time (h)	yield (%)[b]	monomethyl/ dimethyl ratio
1	 **1b**	2.5	69	**2b/3b** 9.4:1
2	 **1c**	2.5	70	**2c/3c** 6.1:1
3	 **1a**	1.5	69	**2a/3a** 3.4:1
4	 **1d**	3	66	**2d/3d** 1:0
5	 **1e**	1.5	72	**2e/3e** 6:1
6	 **1f**	1.5	63	**2f/3f** 3.5:1
7	 **1g**	3.5	59	**2g/3g** 1:0
8	 **1h**	3	70	**2h/3h** 18:1
9	 **1i**	2.5	74	**2i/3i** 38:1

[a] Typical procedure: 1 mmol of amine, 2.5 mmol of methylboronic acid, 2.5 mmol of $Cu(OAc)_2$ and 3.5 mmol of pyridine in dioxane were allowed to react at reflux. [b] Isolated yields represent the average of two runs.

Table 4. Scope and Limitations of Copper-Promoted Monomethylation of Anilines[a]

entry	substrate	time (h)	product (yield)[b]
1	 **1j**	4.5	**2j** (86)
2	 **1k**	4.5	**2k** (78)
3	 **1l**	4.5	**2l** (48)
4	 **1m**	4.5	**2m** (88)
5	 **1n**	2.5	**2n** (80)
6	 **1o**	4.5	**2o** (75)
7	 **1p**	18	**2p** (0)[c]
8	 **1q**	2	**2q** (30)
9	 **1r**	2	**2r** (53)

[a] Typical procedure: 1 mmol of amine, 2.5 mmol of methylboronic acid, 2.5 mmol of $Cu(OAc)_2$ and 3.5 mmol of pyridine in dioxane were allowed to react at reflux. [b] Isolated yields represent the average of two runs. [c] Complex mixture of products was detected.

(DoE) using a common two-factorial model. Optimization experiments involved *p*-toluidine as test substrate. The reaction conversion and percentages of mono- and dimethylated compounds were monitored by HPLC-MS at different times.

The excess of base is not a relevant factor for the coupling: similar conversions arose from using between 3 and 5 equiv of pyridine.

The ratio of copper salt and boronic acid was found to be critical. A mixture composed by 2.5 equiv of $Cu(OAc)_2$ and 2.5 equiv of $MeB(OH)_2$ gave the most efficient cross-coupling rates, while minimizing the amount of dimethylated amine.

Most of the product was formed at the beginning of the reaction, with the formation rate decaying with time (Figure 1). Interestingly, dimethylated compound was obtained in higher yields when longer reaction times were applied. These results suggest that to avoid the formation of the dimethylated compound the reaction must proceed as quickly as possible, since long reaction times allow the product to dimethylate.

(7) Collot, V.; Bovyb, P. R.; Raulta, S. *Tetrahedron Lett.* **2000**, *41*, 9053–9057.

The order of addition of reagents was also crucial to improve conversions: the copper catalyst must be added first and an incubation period (10−15 min) was needed. Otherwise, addition of $MeB(OH)_2$, even at 5 fold-excess, was not enough to get full conversion.

With this optimized reaction conditions in hand, a number of structurally and electronically diverse anilines were subjected to the cross-coupling conditions, to explore the scope and limitations of the transformation (Table 3).

The functional group tolerance is good. The reaction proceeds with both electron-rich and electron-deficient anilines (entries 4−9, Table 3). Sterically demanding ortho substituted anilines required slightly longer reaction times, but they were also efficiently methylated, giving mainly the monomethylated product.

Scope and limitations of the method were explored with more diverse substrates (Table 4). Some compounds that have been problematic in the reductive amination chemistry, such as anilines bearing a ketone or ester moiety, were also successfully transformed (entries 1 and 2, Table 4). The reaction could be also applied to substrates bearing the tioether functional group, that have been shown problematic in some palladium cross-coupling reactions (entry 3, Table 4).

Aryl halides are also tolerated (entries 5 and 6, Table 4). The chemoselective coupling of 3-Br-aniline is interesting for several reasons: it shows that *N*-methylation is favored over possible *N*-arylation processes, and it allows further functionalization of the resulting methylaniline by means of cross-coupling reactions of the aryl halide.

It should be noted that when 3-aminopyridine was submitted to the reaction conditions, no coupling product was obtained (entry 7, Table 4). Aminoquinolines could be methylated, although in low yields (entries 8 and 9, Table 4).

In conclusion, we have developed a novel system for the selective preparation of *N*-methylanilines in good to excellent yields through the cross-coupling of $MeB(OH)_2$ with anilines in the presence of $Cu(OAc)_2$. To our knowledge, the reaction represents the first metal-mediated coupling of a common nitrogen nucleophile with methylboronic acid reported to date. The mild reaction conditions and functional group tolerance make this approach potentially useful for the monomethylation of anilines and other heterocyclic amines in a single step. This procedure further extends the utility of the copper promoted cross-coupling reactions beyond aryl and alkenylboronic acid derivatives.

Further exploration, including mechanistic investigation, making the reaction catalytic, and the extension of the protocol to alkyl groups different from methyl, and other *N*-based nucleophiles, are currently under investigation, and will be reported in due course.

Acknowledgment. We thank the CDTI (Spanish Ministry of Research and Science) for financing this work through the CENIT Genius Pharma project. Our thanks to Dr. Torrens and Dr. Yenes, from Laboratorios Esteve, for supplying us with figures from Integrity (Prous Science).

Supporting Information Available: Experimental procedures and characterization data for all compounds isolated. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802882K

(8) (a) Combs, A. P.; Tadesse, S.; Rafalski, M.; Haque, T. S.; Lam, P. Y. S. *J. Comb. Chem.* **2002**, *4*, 179–182. (b) Chiang, G. C. H.; Olsson, T. *Org. Lett.* **2004**, *6*, 3079–3082. (c) Hayat, S.; Atta-Ur-Rahman; Choudhary, M. I.; Khan, K. M.; Schumann, W.; Baye, E. *Tetrahedron* **2001**, *57*, 9951–9957.

(9) (a) Tsuritani, T.; Strotman, N. A.; Yamamoto, Y.; Kawasaki, M.; Yasuda, N.; Mase, T. *Org. Lett.* **2008**, *10*, 1653–1655. (b) Bénard, S.; Neuville, L.; Zhu, J. *J. Org. Chem.* **2008**, *73*, 6441–6444. (c) For the use of cyclohexylboronic acid, see chapter 5 in *Boronic Acids*, 1st ed.; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005.

(10) For the coupling of organotrifluoroborates with alcohols, see: Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 1381–1384.