Accepted Manuscript

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PII: DOI: Reference:	S0040-4039(13)01113-1 http://dx.doi.org/10.1016/j.tetlet.2013.06.128 TETL 43181		
To appear in:	Tetrahedron Letters		
Received Date:	16 April 2013		
Revised Date:	13 June 2013		
Accepted Date:	26 June 2013		



Please cite this article as: Pedersen, L., Mady, M.F., Sydnes, M.O., One-pot Suzuki-Miyaura cross-coupling followed by reductive monoalkylation of the resulting nitro biaryl system utilizing Pd/C as catalyst, *Tetrahedron Letters* (2013), doi: http://dx.doi.org/10.1016/j.tetlet.2013.06.128

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One-pot Suzuki-Miyaura cross-coupling followed by reductive monoalkylation of the resulting nitro biaryl system utilizing Pd/C as catalyst

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ARTICLE INFO

ABSTRACT

Article history: Received Received in revised form Accepted Available online

Keywords: One-pot Catalysis Pd/C Suzuki-Miyaura cross-coupling Reductive monoalkylation Conditions for one-pot Suzuki-Miyaura cross-coupling between aryl boronic acids and bromonitrobenzene followed by reductive monoalkylation of the nitro functionality of the biaryl crosscoupling product utilizing hydrogen over Pd/C as the catalyst and aldehydes as alkylation agent is described.

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One-pot reactions, where several steps are performed in the same reaction vessel, have gained significant attention from chemists working towards conducting synthesis in a more sustainable fashion.¹ The development of such reactions are therefore important as chemists aim to minimize the use of reagents, catalysts, and solvent, as well as reducing the number of isolation steps which generate additional waste.

Nitro aryls are an important class of compounds due to their easy formation from a range of aromatic starting materials² and their ready conversion into aromatic amines.³ Primary aryl amines are vital starting materials for the preparation of secondary amines found in numerous products, such as pharmaceuticals.⁴ However, the selective conversion of primary amines into secondary amines in high yields still remains a challenge. Several one-pot strategies for the selective synthesis of secondary amines have been reported⁵ including our own efforts towards this end.⁶

The use of Pd/C for ligand free Suzuki-Miyaura crosscoupling reactions has been pioneered by Sajiki and coworkers.^{7,8} Mild conditions are now available for the crosscoupling of boronic acids or boronates with aryl halides (Br, I).^{7,9} In continuation of our work in which Pd/C (10%) was utilized as a catalyst for the reductive monoalkylation of nitro aryls under an atmosphere of hydrogen⁶ we herein report the Suzuki-Miyaura cross-coupling reaction of 1-bromo-4-nitrobenzene prior to reductive monoalkylation of the resulting nitro biaryl compound in the same pot.

Based on the aforementioned successful Suzuki-Miyaura cross-coupling catalyzed by Pd/C, and our earlier reports on

reductive monoalkylation of nitro aryls, it was envisaged that the cross-coupling reaction could be conducted prior to the reductive monoalkylation of the nitro functionality in the Suzuki-Miyaura cross-coupling product. As a starting point for our investigation, the reaction sequence outlined in Scheme 1 was chosen. Based on the work of Sajiki et al.,7b it was envisaged that their conditions for the Pd/C catalyzed Suzuki-Miyaura crosscoupling would be a good starting point for our optimization of the first part of the reaction sequence. Utilizing the same solvent system (EtOH/H₂O, 1:1) and base (Na₂CO₃) as Sajiki and coworkers, and heating the reaction mixture at reflux resulted in expedient cross-coupling, as judged by TLC analysis, over the course of three hours, however, the following reductive monoalkylation sequence conducted at room temperature utilizing ten equivalents of acetaldehyde and hydrogen gas (1 atm) as the reducing agent, failed to proceed over three days according to TLC analysis (entry 1, Table 1). The situation was improved when the water content in the solvent system was reduced (EtOH/H₂O, 3:1) resulting in the isolation of the desired secondary amine 3a in 51% yield in addition to 34% of the corresponding primary amine after 48 hours under a hydrogen atmosphere (entry 2, Table 1). Further reduction of the water content (EtOH/H₂O, 12:1) resulted in the cross-coupling reaction still proceeding smoothly (3 hours), followed by reductive monoalkylation of the nitro biaryl when ten equivalents of acetaldehyde were used, thus resulting in the isolation of the desired product 3a in 95% yield after column chromatography (entry 3, Table 1). Utilizing the latter reaction conditions, but reducing the concentration of acetaldehyde (entries 4 and 5, Table 1) resulted in longer reaction times. After 48 h the predominant product in the reaction mixture was the primary amine together with small amounts of compound 3a according to TLC analysis.

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Scheme 1. Outline of the one-pot reaction sequence (Method A).

Entry	Solvent	Equiv.	Time ^a	Yield
		acetaldehyde		3a
1	EtOH/H ₂ O (1:1)	10	3 h, 96 h	_ ^b
2	EtOH/H ₂ O (3:1)	10	3 h, 48 h	51% ^c
3	EtOH/H ₂ O (12:1)	10	3 h, 48 h	95%
4	EtOH/H ₂ O (12:1)	1.5	3 h, 48 h	_ ^d
5	EtOH/H ₂ O (12:1)	3.3	3 h, 48 h	_ ^d

Table 1. Optimization	of reaction	conditions
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^aThe first time is the time for the Suzuki-Miyaura cross-coupling and the second time reported is the time used for the reductive monoalkylation; ^bNo secondary amine was observed by TLC analysis; ^c34% of the primary amine was also isolated; ^dSmall amounts of compound **3a** were observed by TLC analysis.

During our optimization experiments (Table 1) it was obvious that the water content in the solvent system played an important role during the imine forming step of the reaction. The imine formation did not take place when the EtOH/water ratio is 1:1 (entry 1, Table 1) and slowly improved when the water content was reduced (entries 2 and 3, Table 1). Based on literature reports it is obvious that the sensitivity to water during the imine forming process is substrate dependent,¹⁰ and, as described in our work, small quantities of water are acceptable.

With suitable reaction conditions in hand we embarked upon determining the scope of the one-pot reaction. A range of saturated aldehydes were chosen as alkylating agents together with a few arylboronic acids (see Table 2). Conducting the reaction sequence utilizing saturated aldehydes gave good to excellent yields of the desired products (entries 1-10, Table 2). The reductive monoalkylation process was run until the reaction had reached completion, as judged by TLC analysis, or for a maximum of 48 hours.



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Table 2 One-pot for	ormation of secondary	biaryl amines from 1	-bromo-4-nitrobenzene utili	zing Method A. ^a	
Entry	Boronic acid	Aldehyde	Product	Time ^b	Yield
1		CH ₃ (CH ₂) ₄ CHO		3 h,	76%
				48 h	
	1a		CeH12		
	14		N N H		
			3b		
2	1 a	CH ₃ (CH ₂) ₈ CHO		3 h,	80%
				23 h	
			C ₁₀ H ₂₃		
			Ĥ		0
2	19	~		2 h	800/
5	14			5 ll,	09%
		\rightarrow		40 11	
		СНО	N N		
			H 3d		
4	MeO	CH ₃ CHO	MeO	3 h,	70%
				48 h	
	∽ B(OH) ₂				
	di				
			3e		
5	1b	CH ₃ (CH ₂) ₄ CHO	MeO	3 h,	85%
				24 h	
			C ₆ H ₁₃		
			H		
		^	- 3f		
6	1b		MeO	3 h, 16 h	88%
		ĊНО			
			H 3a		
7		нсно		4 h	99%
,		(formaldehyde		24 h	<i></i>
	B(OH) ₂	solution. 37 wt% in			
	10	water)	N		
			3h		
8	1c	CH ₃ CHO		7.75 h, 48 h	75%
			Et		
			2i		
0	1-		ت 	4 1-	05%
9	чс	СП3(СН2)4СНО		4 N, 24 h	93%
				24 11	
			' [′]		
			⊣ 3j		
10	1c	\frown		4 h,	98%
				24 h	
		СНО			
₩			× N H		
			3k		
11	1a	o		3 h,	23%
		Т СНО		36 h	
		0.10	Ľ ∕ N ∕		
			H 3I		
L	1				

^aSolvent (EtOH/H₂O, 12:1), Suzuki-Miyaura cross-coupling was conducted at reflux, and the reductive monoalkylation was conducted at rt with 10 equiv. of aldehyde (see also Scheme 1); ^bThe times given correspond to the following reactions: Suzuki-Miyaura cross-coupling, reduction + imine formation + reduction.

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Not surprisingly, utilizing 2-furaldehyde as the alkylation agent under the standard conditions (Method A) resulted in a low yield (23%) of the desired product 31 (entry 11, Table 2). Furaldehydes are known to be readily reduced over hydrogen on Pd/C, thus generating a range of products including tetrahydrofuran.¹¹ However, by utilizing the reaction conditions for the reductive monoalkylation developed in our previous work,^{6b} thus conducting the imine formation under an atmosphere of air followed by reduction under an atmosphere of hydrogen, Method B (Scheme 2), it was possible to improve the yield of the desired compound **31** to 49% (entry 1, Table 3). These conditions also facilitated the formation of the furan-2-ylmethyl compounds 3m and 3n in 54% and 59% isolated yields, respectively (entries 2 and 3, Table 3). Although the yields for these conversions were moderate, the method described herein represents an easy way to generate these compounds.



Scheme 2. Outline of Method B.

In conclusion, we have developed simple conditions that facilitate the Suzuki-Miyaura cross-coupling of aryl boronic acids with 1-bromo-4-nitrobenzene prior to reductive monoalkylation of the resulting biaryl nitro compounds in one-pot utilizing Pd/C as catalyst and hydrogen gas (1 atm) as the reducing agent. These conditions resulted in the formation of secondary amines in predominantly good yields when saturated aldehydes were utilized as the alkylation agent. In this one-pot procedure, four sequential reaction steps, Suzuki-Miyaura cross-coupling, reduction of the nitro functionality to the primary amine, imine formation, and reduction of the imine to the corresponding secondary amine occurred in one reaction flask with only one simple purification step. Further work will focus on reducing the equivalents of aldehyde needed for the reaction and also switching the halide in the starting material from bromine to chlorine.

Acknowledgments

Financial support from the University of Stavanger and the research program, Green Production Chemistry is gratefully acknowledged. M. M. is grateful for the provision of a ParOwn grant from the Egyptian government. Thanks are also due to Dr. Bjarte Holmelid, University of Bergen, for recording mass spectra.

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Supplementary Material

Supplementary material available: Experimental procedures, experimental data and NMR spectra of new compounds. See

Table 3 One-pot formation of secondary biaryl amines with 2-furaldehyde utilizing Method B.^a

Tuble 5 One pot 1011	nution of secondary of	yi unines with 2 fututdenyde	utilizing method D.		
Entry	Boronic acid	Product	Time ^b	Yield	
1	1a	3I	3 h, 1.5 h, 4 h, 24 h	49%	
2	16	MeO NH 3m	3 h, 1.5 h, 4 h, 24 h	54%	ó
3	10		3 h, 1.5 h, 4 h, 24 h	59%	

^aSolvent (EtOH), Suzuki-Miyaura cross-coupling was conducted at reflux, and the remaining steps were conducted at rt with 10 equiv. of 2-furaldehyde (see also Scheme 2); ^bThe times given correspond to the following reactions: Suzuki-Miyaura cross-coupling, reduction to primary amine, imine formation (under an atm of air), reduction to the secondary amine.