

Addition of Arylboronic Acids to Symmetrical and Unsymmetrical Azo Compounds

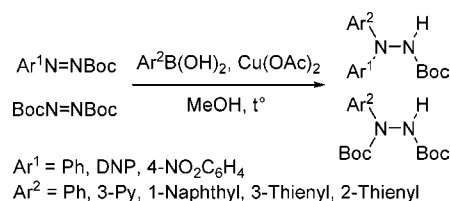
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ABSTRACT



The addition of aryl- and heteroarylboronic acids to azo compounds is described. Copper salt catalysis was necessary to perform the reaction under mild conditions and high yields. Excellent regioselectivity was observed in addition to unsymmetrical azo compounds.

N-Arylation still remains one of the most challenging C–X couplings. Despite the revolutionary achievements of palladium catalysis,¹ classical Ullmann and Goldberg reactions are still very useful² since remarkable improvements have been made to the method in recent years. Copper(I) and -(II) catalysis enables the use of wide scope of reagents as aryl sources. Besides arylhalogenides, the examples include aryltrialkylstannanes,³ arylleadtriacetates,⁴ triarylbi-muthanes/triarylbi-muth diacetates,^{4,5} and boron derivatives, such as readily available arylboronic acids⁶ or aryltrifluoroborate salts.⁷

Arylation of hydrazines, which are a special class of nitrogen compounds, is of high interest because of their

pharmaceutical importance. Both organobismuth reagents^{5b,8} and aryl iodides⁹ were recently used in the preparation of substituted hydrazines, whereas Lan's and Lam's works involved arylboronic acids.^{3,6} All these methods start with a N–H compound, although substituted hydrazines can also be obtained by addition of an aryl-containing nucleophile to azo compound. The analogy is clearly recognized in both the Petasis–Mannich¹⁰ and Liebeskind methods,¹¹ where an N=C or N=O electrophile is used in reaction with arylboronic acids.

Therefore, we decided to combine a copper-catalyzed N-arylation process with addition to the N=N bond in azo

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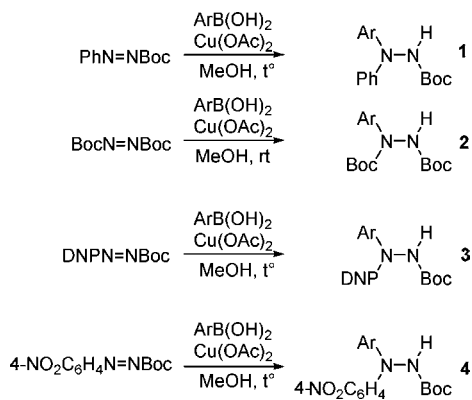
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compounds. The parallel work was very recently reported by Chatani and included azodicarboxylates as electrophile.¹² However, as we were interested in more complicated hydrazine derivatives, our studies are not confined to symmetrical azo compounds.

The starting materials were easily obtained from the corresponding disubstituted hydrazines via oxidation with Br₂/Py¹³ or activated MnO₂ in dichloromethane at room temperature. The reaction is outlined in Scheme 1, and the results are presented in Table 1.

Scheme 1. Reaction between Arylboronic Acids and Different Azo Compounds



PhN=NBoc was used as model compound.¹⁴ The addition of phenylboronic acid (1.1 equiv) proceeded even without catalyst in refluxing methanol (24 h), yielding 71% of Ph₂NNHBoc with traces of PhNHNHBoc as detected on TLC. Catalytic 5 mol % of Cu(OAc)₂·H₂O was essential to

Table 1. Copper-catalyzed Addition of Arylboronic Acids to Azo Compounds

entry	azo compd	aryl	reaction time	yield, %
1a	PhN=NBoc	Ph	1.5 h ^a	100
1b	PhN=NBoc	1-naphthyl	45 min	77
1c	PhN=NBoc	3-Py	6 h	65
1d	PhN=NBoc	2-thienyl	7 h	<i>b</i>
1e	PhN=NBoc	3-thienyl	7 h	<i>b</i>
2a	BocN=NBoc	Ph	30 min	91
2b	BocN=NBoc	1-naphthyl	30 min	60
2c	BocN=NBoc	3-Py	15 min	43
2d	BocN=NBoc	2-thienyl	20 min	45
2e	BocN=NBoc	3-thienyl	40 min	100
3a	DNPN=NBoc ^c	Ph	7–8 min	57 ^d
3b	DNPN=NBoc	3-Py	22 h	18
4a	4-NO ₂ C ₆ H ₄ N=NBoc	Ph	1 h	100
4b	4-NO ₂ C ₆ H ₄ N=NBoc	1-naphthyl	4 h	94
4c	4-NO ₂ C ₆ H ₄ N=NBoc	3-Py	8 h	78
4d	4-NO ₂ C ₆ H ₄ N=NBoc	2-thienyl	16 h	<i>b</i>
4e	4-NO ₂ C ₆ H ₄ N=NBoc	3-thienyl	36 h	59

^a Experiments 1a–e, 2c, and 3a–4e were conducted at reflux, the rest at rt. ^b Only decomposition products. ^c DNP: 2,4-dinitrophenyl. ^d 21% of DNPNNHPhBoc and 21% of DNPNNHBoc were isolated.

substantially increase the yield to quantitative and to decrease the reaction time (2 h in methanol at rt, 1.5 h under reflux). The same arylation in CH₂Cl₂ was complete in 16 h at rt, giving the product in 93% yield. After refluxing the reaction mixture in acetonitrile for 6 days the starting material was recovered in 31% and 45% of product was obtained. Therefore, methanol was considered to be the solvent of choice for this reaction.

The regioselectivity of addition to ArN=NBoc is confirmed by the analysis of ¹H NMR spectra. The signal at 7.0 ppm corresponds to BocNH, and no hypothetical PhNH was detected in the range 5–6 ppm. The melting point of the product Ph₂NNHBoc (122–123.5 °C, from hexane) was in agreement with data reported previously (122.5–124 °C, from cyclohexane).¹⁵ Coupling of PhB(OH)₂ and DNPN=NBoc was the only reaction, where we have isolated the other isomer in 21% yield. The products were distinguished by the signal at 9.46 ppm in ¹H NMR, which belongs to DNPNH in DNPNNHNBoc and DNPNNHPhBoc.

BocN=NBoc was found to be more reactive than PhN=NBoc since all arylations except in the case of with 3-PyB(OH)₂ did not require elevated temperatures and were complete in less than 45 min. On the other hand, coupling of PhN=NBoc with phenylboronic acid was extremely slow under the described conditions.

The addition is not very sensitive to steric hindrance as judged from the short reaction times of 1-naphthylboronic acid. Still, low yields and longer reactions times in the case of 3-PyB(OH)₂ suggest some dependence on the electronic effect of the aryl group. The results obtained with 3-thienylboronic acid are also quite different from those with the isomeric 2-thienylboronic acid.

Coupling of PhN=NBoc with 1-naphthylboronic acid was the only case where we observed positive influence of inert atmosphere (77% under argon versus 55% in the presence of air). BocN=NBoc yielded exactly the same results with 2- and 3-thienylboronic acids under both air and argon atmosphere. In several reactions between thienylboronic acids and azo compounds, the corresponding hydrazines were detected in traces by TLC as the result of a reductive side reaction.

The possible reaction mechanism, as derived from generally accepted considerations, is depicted in Scheme 2.

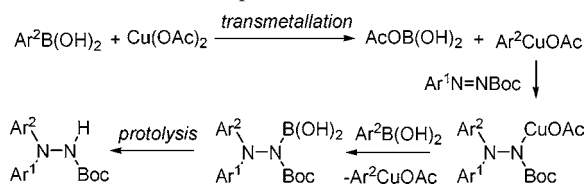
It is interesting that the addition of alkyl/aryl organo-metallic nucleophiles to a row of unsymmetrical azo

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(14) A typical procedure is given, using **1a** as example. The mixture of PhN=NBoc (100 mg, 0.4854 mmol), PhB(OH)₂ (95 mg, 1.6 equiv), and Cu(OAc)₂·H₂O (6 mg, 0.05 equiv) was refluxed in methanol (2 mL). The reaction was monitored by TLC (1: 4 EtOAc–hexane). After starting material was consumed in 1.5 h, silica gel (0.5 g) was added to the mixture and the solvent was removed under reduced pressure. The obtained residue was chromatographed (1:10 EtOAc–hexane), yielding 138 mg (quantitative yield) of white solid Ph₂NNHBoc, pure by TLC and NMR: IR (KBr) ν = 3317 (NH), 1704 (CO) cm⁻¹; ¹H NMR δ = 1.48/1.31 (s, 9H, Boc), 6.87/6.71 (broad s, 1H, NH), 6.9–7.4 (m, 10H, Ph); ¹³C NMR δ = 28.3 (Boc), 81.3 (C_q, Boc), 119.4, 122.7, 129.1, 146.4 (Ph), 155.3 (CO, Boc).

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Scheme 2. Proposed Reaction Mechanism

compounds (PhN=NBoc, PhN=NAc, *o*-CH₃C₆H₄N=NBoc) revealed exactly the same regioselectivity.¹⁶

The same regioselectivity was observed in direct arylation of PhNHNHBoc by PhB(OH)₂/Cu(OAc)₂ in methanol. In the presence of a stoichiometric amount of Cu(OAc)₂, the reaction was complete in 2 h (98% yield). A catalytic amount of Cu(OAc)₂ prolonged the reaction time to 70 h. We have also found that PhNHNHBoc is readily oxidized by Cu(OAc)₂ to the azo compound (half of the material reacted in 30 min, TLC). Thus, we have concluded that arylation of PhNHNHBoc by PhB(OH)₂ proceeds in two steps. First, the oxidation of hydrazine by copper(II) occurs, followed by the

addition of the arylboronic acid to the resulting azo compound. In contrast, slow progress of arylation in the presence of 5% of catalyst can be attributed to the typical direct catalytic NH arylation by PhB(OH)₂ occurring instead of addition to azo compound.

In conclusion, this work reports a systematic study of coupling between arylboronic acids and azo compounds of different structure. Regarding to the recently described regioselective addition of organometallic nucleophiles to unsymmetrical azo compounds, the current reaction can be considered as its useful alternative.¹⁶ Since the practical procedure is very convenient, the method is expected to find applications in the synthesis of multisubstituted protected/arylated hydrazines.

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

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