

## Arylation of substituted hydrazines with arylboronic acids

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**Abstract.** Copper-mediated arylation of di- and trisubstituted hydrazines with aryl- and hetero-arylboronic acids is described. Boronic acids were chosen because of their commercial and synthetic availability and mild reaction conditions of the corresponding C–N cross-coupling reactions.

**Key words:** N-arylation, C–N cross-coupling, arylboronic acid, hydrazine.

Many of hydrazine derivatives are used as agrochemicals, dyestuffs, and pharmaceuticals [1]. Hydrazines are industrially valuable compounds and useful intermediates in the preparation of heterocycles, azapeptides, and aromatic amines [2]. Several hydrazines have been found to be active substances for the treatment of severe diseases. As a consequence the increasing interest in the aryl- and heteroarylsubstituted hydrazines can be noticed nowadays [3–7].

Katritzky and co-workers [4] have published a method for efficient synthesis of arylhydrazines, which envisages the use of symmetric diazocompounds. Therefore the procedure can be used to prepare just trisubstituted hydrazines with two identical and one different aryl groups [4].

Other methods are based on direct N-arylation. First of all, Pd-catalysis has been widely used in the arylation of amines and was also applied on hydrazines [5]. The laborious optimization of the catalytic process and harsh reaction conditions are disadvantages of this technique.

Descriptions of Cu-mediated N-arylation with triarylbi-muth compounds (see [6] for references) and arylboronic acids [8] have been published. Both of these reactions occur in mild conditions. In the synthesis of substituted hydrazines amino-protecting groups were used to achieve high selectivity. Our group

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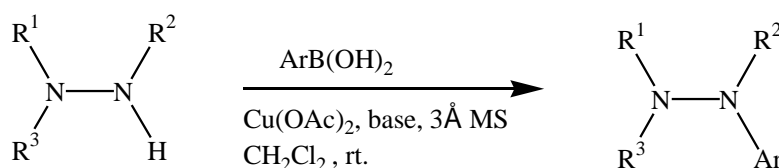
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synthesized and arylated a large number of protected hydrazine derivatives with tri- and pentavalent arylbismuth compounds [6, 7].

The purpose of the current study was to find a method for introducing pyridyl and other heteroaryl groups into hydrazine molecules. Unfortunately, the synthesis of tri-(3-pyridyl)bismuth was not successful. Unlike bismuth compounds many heterocyclic boronic acids are commercially available or easy to prepare [9].

We investigated the influence of the structure of the substrate, arylboronic acid, and base on the yield of arylated hydrazines (Scheme 1). The data on the arylation of some di- and trisubstituted hydrazines with phenyl-, 3-pyridyl-, and 2-thienylboronic acids are presented in Table 1.

Best results were obtained in the arylation of 1,2-di-Boc-hydrazine. In three days the starting material was fully consumed. The chromatographical work-up furnished the product in a good yield. Attempts to arylate unsymmetrical disubstituted hydrazines such as 1-Tos-2-Z-hydrazine resulted in the formation of complex mixtures. Probably the competing formation of an azo compound occurs in the presence of  $\text{Cu}(\text{OAc})_2$ . In the arylation of 1-Tos-2-Z-hydrazine the consumption of the starting material was much faster (1–2 hours) than in the case of 1,2-di-Boc-hydrazine.



**Scheme 1.** Arylation of substituted hydrazines with arylboronic acids.  $\text{R}^1 = \text{Boc, Toc}$ ;  $\text{R}^2 = \text{Boc, Z}$ ;  $\text{R}^3 = \text{H, CH}_3, \text{Boc, Toc}$ ;  $\text{Ar} = \text{Ph, Py, thienyl}$ ;  $\text{Boc} = \text{tert-butylcarbonyl}$ ;  $\text{Tos} = p\text{-methylphenyl-sulfonyl}$ ;  $\text{Z} = \text{benzyloxycarbonyl}$ ;  $\text{Py} = 3\text{-pyridil}$ .

**Table 1.** Arylation of substituted hydrazines with arylboronic acids

Entry	Substrate	Reagent	Base	Time	Yield, %
1	BocNH–NHBoc	PyB(OH) <sub>2</sub>	TEA <sup>a</sup>	3 days	74 <sup>b</sup>
2	BocNH–NHBoc	PyB(OH) <sub>2</sub>	Py	3 days	– <sup>b, c</sup>
3	BocNH–NHBoc	PhB(OH) <sub>2</sub>	TEA <sup>a</sup>	3 days	59
4	BocNH–NHBoc	PhB(OH) <sub>2</sub>	1,10-phenantroline	3 days	27
5	TosNH–NHZ	PhB(OH) <sub>2</sub>	TEA <sup>a</sup>	2 hours	– <sup>c</sup>
6	(Boc) <sub>2</sub> N–NHBoc	PhB(OH) <sub>2</sub>	TEA <sup>a</sup>	4 days	– <sup>d</sup>
7	BocTosN–NHZ	PhB(OH) <sub>2</sub>	TEA <sup>a</sup>	4 days	32 <sup>d</sup>
8	BocMeN–NHBoc	PhB(OH) <sub>2</sub>	TEA <sup>a</sup>	4 days	29 <sup>d</sup> (16 <sup>b</sup> ) <sup>d</sup>
9	BocMeN–NHBoc	ThienylB(OH) <sub>2</sub>	TEA <sup>a</sup>	4 days	10 <sup>d</sup>
10	BocMeN–NHBoc	ThienylB(OH) <sub>2</sub>	Py	4 days	0

<sup>a</sup> TEA = triethylamine.

<sup>b</sup> No molecular sieves were added.

<sup>c</sup> Several products were obtained.

<sup>d</sup> After 1 or 2 days the extra 0.5 eq. of  $\text{Cu}(\text{OAc})_2$ , arylboronic acid and base were added.

Steric hindrance seems to play an important role in the derivatization of trisubstituted hydrazines (entries 6–8). In the reaction with 1,1,2-tri-Boc-hydrazine only traces of the product were detected by TLC and most of the starting material remained unreacted. Addition of extra phenylboronic acid,  $\text{Cu}(\text{OAc})_2$  and TEA, or raising the temperature did not give any detectable progress in reaction. Other trisubstituted hydrazines gave modest yields of arylated products. As it can be observed from entry 7, addition of molecular sieves improves the yield. Molecular sieves absorb water formed from the aryl boronic acids during the arylation and therefore favour the arylation. Among the tested bases TEA seems to be the best choice for the arylation of the hydrazines tested.

The preliminary results seem to be very promising, thus giving a new opportunity for the synthesis of heteroaryl substituted hydrazines. Still, the arylation conditions need further optimization.

### **GENERAL PROCEDURE. ARYLATION OF SUBSTITUTED HYDRAZINES**

To the oven-dried flask with 2 eq. of  $\text{ArB}(\text{OH})_2$ , 1 eq. of  $\text{Cu}(\text{OAc})_2$ , 1 eq. of hydrazine derivative, and 3 Å molecular sieves (about 50 mg per 0.1 mmol of hydrazine) was weighed. Then 2 mL of  $\text{CH}_2\text{Cl}_2$  and 2 eq. of base were added and the reaction mixture was stirred at room temperature for 3–4 days. The reactions were monitored by TLC and the products were separated using column chromatography. The structures of compounds were confirmed by NMR spectroscopy:

Entry 1. BocNHNPyBoc

$^1\text{H}$  TMR ( $\text{CDCl}_3$ ):  $\delta = 1.49, 1.50$  (18H, 2 × Boc), 7.1–8.2 (4H, Py).

Entry 7. BocTosNNZPh

$^1\text{H}$  TMR ( $\text{CDCl}_3$ ):  $\delta = 1.33$  (9H, Boc), 2.38 (3H,  $\text{C}_6\text{H}_4\text{CH}_3$ ), 5.31 (2H,  $\text{PhCH}_2$ ), 7.0–7.7 (14H, 2Ph +  $\text{C}_6\text{H}_4$ ).

Entry 8. BocMeNNPhBoc

$^1\text{H}$  TMR ( $\text{CDCl}_3$ ):  $\delta = 1.46, 1.52$  (18H, 2 × Boc), 3.11 (3H, Me), 7.2–7.8 (5H, Ph).

Entry 9. BocMeNN(thienyl)Boc

$^1\text{H}$  TMR ( $\text{CDCl}_3$ ):  $\delta = 1.45$  (9H, Boc), 3.15 (3H, Me), 6.85, 7.55, 7.70 (3H, m, thienyl).

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## Asendatud hüdrasiinide arüülimine arüülboorhapetega

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On uuritud mõnede di- ja triasendatud hüdrasiinide vase sooladega vahendatud arüülimist arüülboorhapetega. Antud meetodi valik tuleneb sellest, et paljusid boorhappeid on võimalik osta ja neid on ka kerge sünteesida. Lisaks sellele kulgeb N-arüülimine arüülboorhapetega pehmetes tingimustes.