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Synthesis of Diprotected Monosubstituted Hydrazine Derivatives from *tert*-Butyl Carbazates and Boronic Acids

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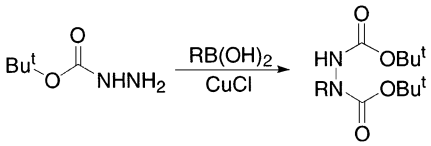
ABSTRACT



Diprotected monosubstituted hydrazine derivatives have been prepared via the reaction of *tert*-butyl carbazates with boronic acids catalyzed by cuprous chloride at room temperature.

Diprotected monosubstituted hydrazine derivatives are versatile intermediates in the synthesis of aromatic amines,[1] aryl hydrazines,[2] substituted hydrazine derivatives,[3] azatides,[4] and β-strand mimics.[5] These products are used in the preparation of a wide variety of biologically and industrially valuable compounds.[3a,f,g,6] Monosubstituted hydrazines are also intermediates in the preparation of heterocyclic compounds such as pyrazoles,[7a] indazoles,[7b] imidazolinones,[7c] and cinnolines.[7d] 2-Heteroaryl hydrazines[8] are interesting synthetic targets due to their efficiency as ligands for a variety of metal complexes.[9] Boc- or trichloroethoxycarbonyl (Troc)-protected aryl hydrazines are generally prepared by electrophilic amination[1,7b,10] of electron-rich arenes utilizing dialkyl

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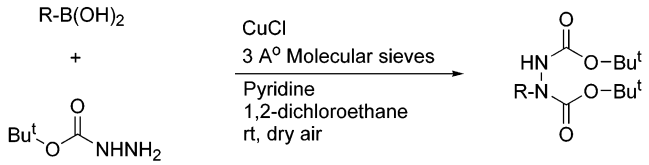
azodicarboxylates. But the methods are suitable only for electron-rich arenes, and rather stringent conditions are often required (thermal heating or microwave irradiation). In addition, dialkyl azodicarboxylates are costly and their preparation can be tedious.[11] Organometallic reagents (lithium,[2b,12a] magnesium,[2b] and zinc[12b]) also react with dialkyl azodicarboxylates to produce substituted hydrazine derivatives. Ragnarsson developed several methods[3b−f] for the multistep syntheses of Boc-protected alkyl and aryl hydrazines using *tert*-butyl or benzyl carbazate.

Organoboronic acids comprise a family of organometallic reagents that tolerate a wide range of functional groups. They are becoming increasingly important in organic synthesis. For example, they have been used to *N*-arylate a variety of important amines and amides.[13] In addition, they are widely available, generally eco-friendly, relatively inert to air and water, and thermally stable. Boronic acids are readily handled without special precautions. As a part of an ongoing research program focused on the use of boronic acids in organic synthesis,[14] we investigated the regioselective *N*-aryl- and *N*-alkylation of *tert*-butyl carbazate with boronic acids. We report the results of this study (Scheme 1).

Scheme 1



R = Aryl, heteroaryl, alkenyl

In our initial experiments, *tert*-butyl carbazate was mixed with phenylboronic acid in the presence of copper(I) chloride, molecular sieves, and pyridine in 1,2-dichloroethane. Di-*tert*-butyl *N*-phenylhydrazodiformate was formed in modest yield. Utilizing 2 equiv of *tert*-butyl carbazate and running the reaction in dry air[13b−f] improved the yield. Carrying out the reactions in an oxygen atmosphere decreased the yield due to formation of aromatic alcohols as side products. Optimal yields were obtained utilizing *tert*-butyl carbazate (2.0 mmol), boronic acid (1.1 mmol), CuCl (0.1 mmol), molecular sieves (500 mg), and pyridine (4.0 mmol) in dry air at room temperature. 1,2-Dichloroethane was found to be a more effective solvent than dichloromethane, DMF, THF, toluene, or MeCN. Elimination of the molecular sieves led to reduced yields and slower reactions. A survey of various catalysts (Table 1) revealed CuCl to be the most effective.

A wide range of substrates including aryl, heteroaryl, and vinylboronic acids readily underwent reaction with *tert*-butyl carbazate to produce protected aryl, heteroaryl, and alkenyl hydrazines in good to high yields (Table 2).

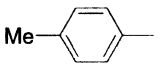
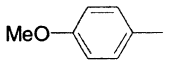
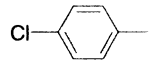
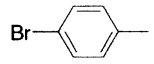
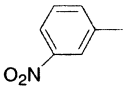
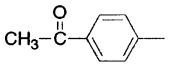
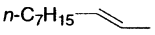
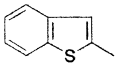
Alkylboronic acids were found to be unreactive. Functional groups such as methoxy, chloro, bromo, nitro, and acetyl

Table 1. Survey of Catalysts for the Reaction of *tert*-Butyl Carbazate with Phenylboronic Acid[a]

catalyst	reaction time (h)	yield[b] (%)
CuCl	24	81
$CuBr·SMe_2$	24	51
CuI	24	42
$CuCl_2$	24	45
$Cu(OAc)_2$	24	22
$Pd(OAc)_2$[c]	24	8

[a] Reaction conditions: *tert*-butyl carbazate (2.0 mmol), phenylboronic acid (1.1 mmol), catalyst (0.1 mmol), 3 Å molecular sieves (500 mg, freshly activated), pyridine (4.0 mmol), 1,2-dichloroethane (3 mL), rt, dry air. [b] Isolated yields. [c] 5 mol % used.

Table 2. CuCl-Catalyzed Reaction of *tert*-Butyl Carbazate with Organoboronic Acids (Scheme 1)[a]

entry	R	time (h)	product yield (%)[b]
1	Ph	24	81
2		24	80
3		24	77
4		36	79
5		45	74
6		6	87
7		7	63
8		96	72
9		44	70
10		72	66
11		48	69
12		60	63

[a] Reaction conditions: *tert*-butyl carbazate (2.0 mmol), boronic acid (1.1 mmol), CuCl (0.1 mmol), 3 Å molecular sieves (500 mg, freshly activated), pyridine (4.0 mmol), 1,2-dichloroethane (3 mL), rt, dry air. [b] Isolated yields.

were unaffected by the reaction conditions. It is noteworthy that the reaction is insensitive to the electronic nature of the functional groups present in the arylboronic acids. Sterically hindered, ortho-substituted (entry 8), alkenyl (entry 9), and heteroaryl boronic acids (entries 10−12) readily participate in the reaction. A series of experiments were performed to gain insight into the reaction mechanism. In the absence of boronic acid, di-*tert*-butyl hydrazodiformate was formed exclusively. In a separate experiment, phenylboronic acid was found to react with di-*tert*-butyl hydrazodiformate to produce an 83% yield of the expected product. These results suggest that the reaction proceeds via self-coupling of the *tert*-butyl carbazate to form di-*tert*-butyl hydrazodiformate which then is arylated by the boronic acid. Presumably, the copper coordinates with the hydrazine intermediate followed by transmetalation with the arylboronic acid. Molecular oxygen could then oxidize the copper in the complex to Cu(III), facilitating reductive elimination of the coupled product.[13b,f,15] Further mechanistic investigations are underway.

Most of the methods available for the synthesis of diprotected aryl hydrazines (Boc or Troc) involve the use of di-*tert*-butyl azodicarboxylate or bis(2,2,2-trichloroethyl) azodicarboxylate. Although commercially available, they are more expensive than *tert*-butyl carbazate.[11] The new reaction, a one-pot synthesis starting from *tert*-butyl carbazate, is simpler than the multistep syntheses currently available.[3b−e]

In conclusion, we have developed a novel method for the synthesis of Boc-protected monosubstituted hydrazine derivatives from boronic acids and *tert*-butyl carbazate. The new protocol has the advantages that Boc-protected monosubstituted hydrazines can be prepared in one step, the reaction tolerates a wide variety of functional groups, proceeds at room temperature, and provides good yields from readily accessible starting materials. Further investigations are in progress.

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Supporting Information Available: General experimental procedure and ^{1}H, ^{13}C and elemental analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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