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Copper-catalyzed synthesis of aryl azides and 1-aryl-1,2,3-triazoles from boronic acids

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Abstract—A catalytic method was developed to synthesize aryl and vinyl azides from the corresponding boronic acids under mild and operationally simple conditions. In addition, a new one-pot procedure was developed to synthesize 1-aryl- and 1-vinyl-1,2,3-triazoles directly from boronic acids and alkynes, which avoided the need to isolate unstable azide intermediates.

Aryl and vinyl azides are useful intermediates in the synthesis of various heterocyclic compounds and transition metal complexes.[1–3] More recently they have also been utilized to constitute important components in many functional materials such as the photoaffinity labelling agents for proteins.[4] Despite these interesting applications, very few synthetic methods have been developed to synthesize aryl and vinyl azides from readily available starting materials.[5] Therefore, at the present time these types of compounds are still prepared mainly by using an old-fashioned and inconvenient approach, that is, replacement of diazonium salts by inorganic azides.

To improve the synthesis of aryl and vinyl azides, Zhu and Ma reported in 2004 a very interesting and creative method in which a copper catalyst was developed to promote the coupling of aryl and vinyl iodides with sodium azides.[6] On the basis of this finding several groups subsequently developed one-pot synthetic methods for the preparation of 1-aryl-1,2,3-triazoles directly from aryl iodides, sodium azide, and terminal alkynes.[7–9] The significance of these studies is manifested by the fact that 1,2,3-triazoles have recently found widespread use in pharmaceuticals and agrochemicals.[10,11] Nonetheless, it is worth noting that the above methods usually suffer from long reaction times (~overnight) even at elevated temperature (~70 °C) due to the slow azidonation of aryl halides.[7–9]

In the present study we sought to further improve the one-pot synthesis of 1-aryl-1,2,3-triazoles by using alternative starting materials to replace the aryl halides. As a result we became interested in the recent discovery by Lam et al., who reported that aryl boronic acids could be coupled to a variety of organic nucleophiles mediated by copper acetate.[12] An important advantage of this method is that much milder reaction conditions are allowed (such as room temperature, aerobic environment, and moisture-containing solvent). Furthermore, the fact that many aryl and vinyl boronic acids are now commercially available makes this method more practically appealing, particularly for generation of combinatorial synthesis of triazole libraries.

Noteworthy, a number of N-centered nucleophiles such as amines, amides, imides, carbamates, and sulfonamides have been previously reported to be utilizable in the coupling reaction with boronic acids.[13] Nevertheless, none of the previous studies has considered the use of an inorganic salt such as sodium azide as the nucleophile. Thus, in order to find out whether the coupling reaction could proceed with an inorganic azide, we designed an array of reaction conditions in a systematic fashion (Table 1). To our great satisfaction, we found that the proposed azidonation reaction occurred smoothly in the presence of several different Cu salts including $Cu(OAc)_2$, $CuSO_4$, CuI, and CuCl. The highest isolated yield (93%) was obtained with 10 mol % of $CuSO_4$ catalyst in MeOH (entry 2). The addition of water to the reaction media decreased the yield to 69% (entry 8). On the other hand, less polar solvents such as dichloromethane could not be used to mediate the

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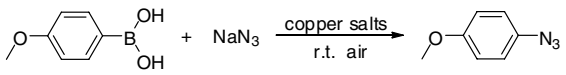
Table 1. Copper catalyzed coupling between 4-methoxyphenylboronic acid (**1**) and sodium azide[a]



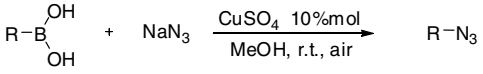
Entry	Boronic acid (mmol)	NaN_3 (mmol)	Catalyst (mol %)	Solvent (3 mL)	Time (h)	Yield[a] (%)
1	1.0	1.5	$Cu(OAc)_2 \cdot H_2O$ (10)	MeOH	5	91
2	1.0	1.5	$CuSO_4$ (10)	MeOH	5	93
3	1.0	1.5	CuI (10)	MeOH	5	93
4	1.0	1.5	CuCl (10)	MeOH	5	91
5	1.0	1.5	$CuSO_4$ (10)	DCM	5	Trace
6	1.0	1.5	$CuSO_4$ (10)	THF	5	Trace
7	1.0	1.5	$CuSO_4$ (10)	EtOH	5	65
8	1.0	1.5	$CuSO_4$ (10)	$MeOH/H_2O = 1:1$	5	69
9	1.0	1.5	$CuSO_4$ (10)	H_2O	5	50
10	1.0	1.5	$CuSO_4$ (20)	MeOH	5	93
11	1.0	1.5	$CuSO_4$ (5)	MeOH	5	76
12	1.0	1.2	$CuSO_4$ (10)	MeOH	5	93
13	1.0	1.1	$CuSO_4$ (10)	MeOH	5	89
14	1.0	1.0	$CuSO_4$ (10)	MeOH	10	84

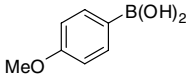
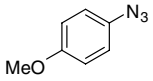
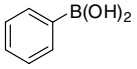
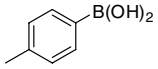
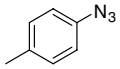
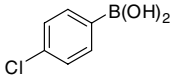
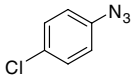
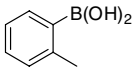
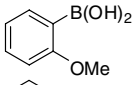
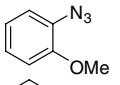
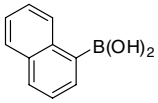
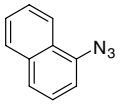
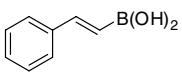
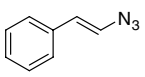
[a] Isolated yield.

coupling reaction (entry 5). It is important to note that the present reaction was accomplished at room temperature and in the air, in contrast to the conditions for the azidonation of aryl halides where the reaction had to be performed at elevated temperature under inert gas protection.[6]

The above results demonstrated that $CuSO_4$ constituted an efficient catalyst for the cross coupling of aryl boronic acid with sodium azide under mild reaction conditions. In order to examine the scope of this newly discovered reaction, we next examined the isolated yields for the cross coupling of a number of representa-

Table 2. Copper catalyzed cross-coupling between sodium azide and various aryl and vinyl boronic acids[a]

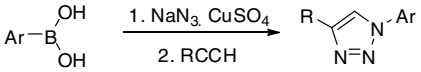


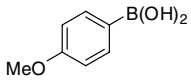
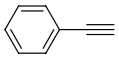
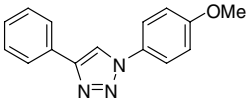
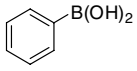
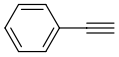
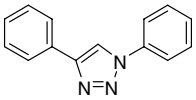
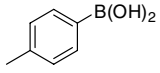
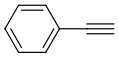
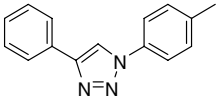
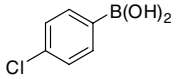
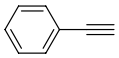
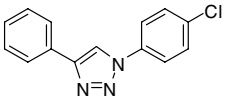
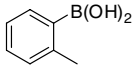
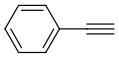
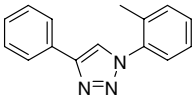
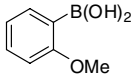
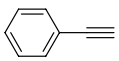
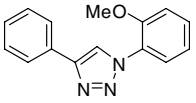
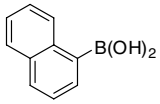
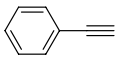
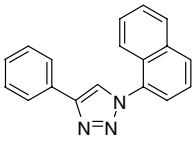
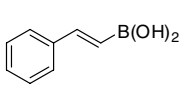
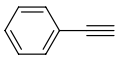
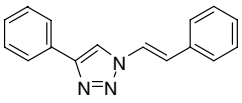
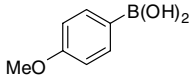
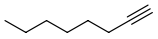
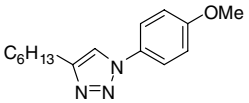
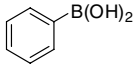
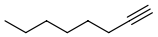
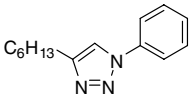
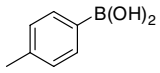
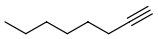
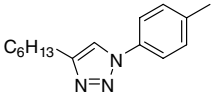
Entry	Reactant	Product	Time (h)	Yield[b] (%)
1			5	93
2			14	90
3			14	92
4			24	70
5			14	92
6			5	90
7			5	98
8			14	86

[a] Conditions: Boronic acid = 1.0 mmol, NaN_3 = 1.2 mmol, $CuSO_4$ = 10 mol %, MeOH = 3 mL, room temperature, in air.
[b] Isolated yield.

tive aryl and vinyl boronic acids with sodium azide (Table 2). It was found that both the electron-rich (i.e., 4-methoxyphenyl-boronic acid) and electron-poor (4-chlorophenyl-boronic acid) substrates could be efficiently converted to the desired products in high yields (entries 1–4). Furthermore, sterically hindered substrates could be well tolerated to some degree since 2-substituted aryl boronic acids could also provide the desired products in over 90% yields (entries 5–6). In addition to the phenyl boronic acids, other aromatic substrates were also utilizable such as naphthalen-1-ylboronic acid (entry 7). Finally, vinyl boronic acids such as (*E*)-styrylboronic acid could be successfully converted to vinyl azides using the same approach (entry 8). Again, we need to stress that these reactions were achieved under very mild conditions at room temperature, in an aerobic environment, and without requirement for any anhydrous solvent. This represented a

Table 3. Copper-catalyzed one-pot synthesis of 1-aryl- and 1-vinyl-1,2,3-triazoles from boronic acids[a]



Entry	Boronic acid	Alkyne	Product	Time	Temperature	Yield[b] (%)
1				12	rt	95
2				17	rt	92
3				17	rt	95
4				41	rt	63
5				33	rt	81
6				12	rt	92
7				12	rt	96
8				17	rt	64
9				15	rt	96
10				20	rt	90
11				20	rt	93

[a] Conditions: Boronic acid = 1.0 mmol, NaN_3 = 1.1 mmol, $CuSO_4$ = 10 mol %, MeOH = 3 mL, water = 3 mL, room temperature, in air.
[b] Isolated yield.

valuable improvement over the previously reported Cu-catalyzed azidonation reaction of aryl halides which had to be performed at elevated temperature under inert gas protection.[6]

Having successfully developed a new and mild method for the preparation of aryl and vinyl azides,[14] we next sought to develop a new one-pot protocol to synthesize 1-aryl- and 1-vinyl-1,2,3-triazoles. Such a one-pot approach is considered to be valuable because organic azides are often unstable to heat and light. Thus, a methodology that avoids the isolation of organic azides is desirable. Previous studies have shown that aryl iodides could be used to couple with sodium azide and an alkyne to afford the triazoles.[7–9] In our approach, we attempted to utilize both aryl and vinyl boronic acids as the starting material. The following one-pot experiments were carried out with an aryl boronic acid (1 equiv), a terminal alkyne (1.1 equiv), NaN_3 (1.1 equiv), and $CuSO_4$ (0.1 equiv) at room temperature.[15] The products were normally obtained by simple filtration. As seen in Table 3, both aromatic and aliphatic alkynes could be used in this one-pot reaction. Besides, a variety of functional groups on aryl and alkenyl boronic acids were fully tolerated. It is significant to note that even sterically hindered aryl boronic acids carrying an *ortho* substituent (entries 5–6) could be successfully converted to the desired product in high yields. In comparison to our approach, the previous one-pot method using aryl iodides was found to be unsuccessful with sterically hindered starting materials (i.e., *ortho*-substituted aryl iodides) even at a high temperature.[8] This evidently shows the advantage of using boronic acids as the starting material where both the reaction condition and scope were better than the aryl halide case.

To conclude, in the present study we reported a novel synthesis of aryl and alkenyl azides from the corresponding boronic acids. Compared to the very recent procedures using aryl halides, our new method showed a milder reaction condition and improved substrate tolerance. On the basis of this finding, we next developed a one-pot procedure to prepare 1-aryl- and 1-vinyl-1,2,3-triazoles directly from boronic acids and alkynes. This one-pot method was advantageous not only because it was operationally simple and high yielding, but also because it completely avoided the isolation of relatively unstable aryl and vinyl azides. Given the fact that many aryl and vinyl boronic acids have now become commercially available,[16] we anticipate that the synthetic method described in the present report will be found useful in a number of fields such as pharmaceutical research and organic material design, where the triazole-type compounds have recently found extensive applications.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.107.

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14. *Typical experimental procedure for the azidonation reaction*: NaN_3 (78 mg, 1.2 mmol) and $CuSO_4$ (0.1 mmol, 16 mg) were placed in an oven-dried round-bottomed flask. Subsequently methanol (3 mL) and boronic acids (1.0 mmol) were added. The reaction mixture was stirred vigorously at room temperature for a certain time (monitored by TLC analysis). The resulting mixture was concentrated in vacuo, and the residue was extracted with petroleum ether or purified by a pad of silicon gel to give the desired aryl or vinyl azide.
15. *Typical experimental procedure for the one-pot triazole synthesis*: NaN_3 (78 mg, 1.2 mmol), $CuSO_4$ (0.1 mmol, 16 mg), and boronic acids (1.0 mmol) were reacted in methanol (3 mL) as described above for 5–14 h. Then water (3 mL), sodium ascorbate (0.5 mmol), and phenylacetylene (1.1 mmol) were added into the reaction mixture. The resulting mixture was stirred vigorously at room temperature for 2–4 h (as monitored by TLC analysis). Some precipitate was formed and collected by a simple filtration. After the precipitate was washed with water (3×25 mL), it was dried in air or further purified by flash chromatography to afford the pure product.
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