A Microwave-Assisted Three-Component Synthesis of Arylaminomethyl Acetylenes: A Facile Access to Terminal Alkynes

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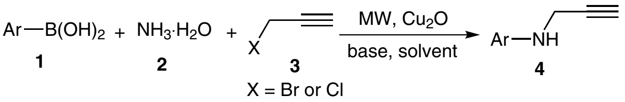
Abstract: A simple, rapid, one-pot synthesis of arylaminomethyl acetylenes is achieved under microwave-assisted conditions (power = 5 W) using aromatic boronic acids, aqueous ammonia, propargyl halides, copper(I) oxide and water as the solvent. The reactions are complete within ten minutes affording good to excellent yields of the products.

Key words: microwave-assisted, three-component, ammonia, propargyl halide, terminal alkynes

Terminal alkynes are used widely in the fields of pharmaceuticals, agrochemicals, functional materials, and organic synthesis.[1] Their utilization in a wide range of cycloaddition[2] and coupling reactions[3] has stimulated a significant level of interest from chemists.

Terminal alkynes can be synthesized from carbonyl compounds via chain extension. The most frequently used reagents for converting aldehydes into terminal alkynes are carbon tetrabromide–triphenylphosphine (CBr_4–Ph_3P), trichloroacetic acid–tosyl chloride (Cl_3CCO_2H–TsCl), and the Bestmann–Ohira reagent and its analogs, in which superbases such as butyllithium (BuLi), sodium hexamethyldisilazide (NaHMDS), and potassium *tert*-butoxide (*t*-BuOK) are usually employed at low temperatures.[4] Acid chlorides can be converted into their corresponding alkynes when combined with a phosphorane reagent, followed by flash-vacuum pyrolysis at a high temperature of 750 °C.[5] Esters and Weinreb amides are also good substrates, which undergo reduction, followed by a one-pot conversion into terminal alkynes.[6] Furthermore, the dehydrobromination of 1- or 2-bromo-1-alkenes is a convenient method developed for this purpose.[7] In this procedure, both *trans*- and *cis*-configured substrates can be converted into terminal alkynes. The direct introduction of the C≡CH residue into arenes and hetarenes through transition metal catalyzed cross-coupling reactions can generate the desired products. In this process, alkyne-containing substrates such as acetylene, trimethylsilylacetylene, propiolic acid, and ethynyltributyl stannane, are often used.[8] In 2011, Huang found that the cleavage of 4-aryl-2-methyl-3-butyn-2-ols, catalyzed by tetrabutylammonium hydroxide, enabled the preparation of terminal arylacetylenes.[9] This method represents a rapid and efficient synthetic route, but the substrates themselves are rare.

Inspired by Fu's preparation of primary aromatic amines by coupling aromatic boronic acids with aqueous ammonia,[10] we herein report a convenient and efficient microwave-assisted (MW) three-component synthesis of arylaminomethyl acetylenes **4** via the coupling of aromatic boronic acids **1**, aqueous ammonia **2** and propargyl halides **3** catalyzed by copper(I) oxide (Cu_2O) in water as the solvent (Scheme 1).



Scheme 1 Synthesis of arylaminomethyl acetylenes **4**

The reaction of *p*-tolylboronic acid (**1a**) (0.5 mmol), ammonia (**2**) (0.6 mmol, 25% aqueous solution), propargyl bromide (**3**, X = Br) (0.5 mmol), base (1 mmol), copper(I) oxide, and solvent (2 mL) under microwave-assisted conditions was chosen as a model system (Table 1).

The application of microwave irradiation had an obvious effect on the reaction rate of this coupling procedure, as shown in Table 1. Under conventional heating at 70 °C, the reaction took more than six hours to form the target molecule in 50% yield (Table 1, entry 1). On using microwave irradiation, the reaction proceeded smoothly and was complete within 10 minutes, affording a higher yield of 63% (Table 1, entry 2). The reaction favored polar solvents such as dimethyl sulfoxide, *N*,*N*-dimethylformamide, and water, and satisfactory yields were observed (Table 1, entries 1, 2 and 6–13), whereas no product was detected when 1,2-dichloroethane or toluene were used as the solvent (Table 1, entries 3 and 4). A microwave power of 5 W was utilized, which proved to be better than lower or higher powers with regard to the yield (Table 1, entries 6–10). The use of other bases had different effects on the formation of the terminal alkyne (Table 1, entries 11–14). Also, decreasing or increasing the amount of copper(I) oxide proved unfavorable to the yields (Table 1, entries 15 and 16). The reaction proceeded more efficiently when promoted by microwave irradiation (power = 5 W) in water, for 10 minutes, catalyzed by copper(I) oxide and using potassium carbonate (K_2CO_3) as the base. The corresponding product, 4-methyl-*N*-(prop-2-ynyl)aniline

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Table 1 Optimization of the Synthesis of 4-Methyl-*N*-(prop-2-ynyl)aniline (**4a**)

Entry	Solvent	Base	Cu_2O (equiv)	MW power (W)	Time (min)	Yield (%)[a]
1[b]	DMSO	K_2CO_3	0.1	–	>360	50
2	DMSO	K_2CO_3	0.1	5	10	63
3	DCE	K_2CO_3	0.1	5	10	–[c]
4	PhMe	K_2CO_3	0.1	5	10	–[c]
5	DMF	K_2CO_3	0.1	5	10	62
6	H_2O	K_2CO_3	0.1	5	10	85
7	H_2O	K_2CO_3	0.1	3	15	82
8	H_2O	K_2CO_3	0.1	2	30	79
9	H_2O	K_2CO_3	0.1	8	7	71
10	H_2O	K_2CO_3	0.1	10	5	70
11	H_2O	Cs_2CO_3	0.1	5	10	78
12	H_2O	$Na_2C_2O_4$	0.1	5	10	72
13	H_2O	KOAc	0.1	5	30	49
14	H_2O	Et_3N	0.1	5	30	31
15	H_2O	K_2CO_3	0.05	5	10	70
16	H_2O	K_2CO_3	0.2	5	10	75

[a] Yield of isolated product.

[b] This reaction was conducted by conventional heating at 70 °C without microwave irradiation.

[c] No reaction.

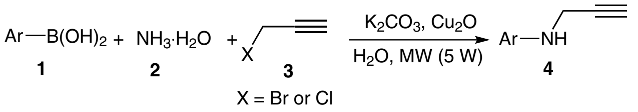
(**4a**), was isolated in 85% yield under these optimized conditions (Table 1, entry 6).

Next, a series of aromatic boronic acids **1** were subjected to this reaction with ammonia (**2**) and propargyl bromide (**3**, X = Br) using the optimized conditions. All the reactions were complete within 10 minutes, and moderate to excellent yields of arylaminomethyl acetylenes **4** were obtained (Table 2). Moreover, propargyl chloride (**3**, X = Cl) also served as the terminal alkyne substrate to afford good yields of the expected products.

The reactions of aromatic boronic acids containing electron-donating groups, such as methyl and methoxy, proceeded with higher yields (Table 2, entries 1 and 3) compared with those containing electron-withdrawing groups, such as chloro, bromo, iodo and nitro (Table 2, entries 4–11). Notably, aromatic boronic acids possessing either an electron-donating or an electron-withdrawing group at the *para* position provided excellent yields of the expected products (Table 2, entries 1, 3, 4, 8 and 9). Although substrates containing an *ortho*-substituent provided lower yields, the reactions were complete within 10 minutes (Table 2, entries 6 and 10).

To investigate further the scope of this procedure, aniline and *n*-pentylamine were selected instead of ammonia as the nitrogen-containing substrate. Unfortunately, the corresponding target molecules were not formed and further work is ongoing in this area.

Table 2 Synthesis of Arylaminomethyl Acetylenes **4**[a]



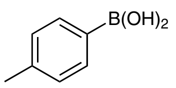
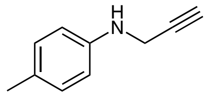
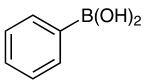
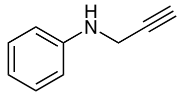
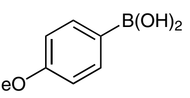
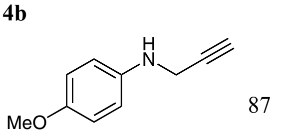
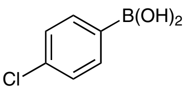
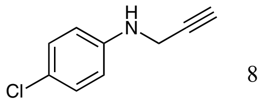
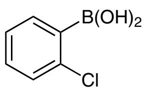
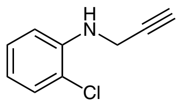
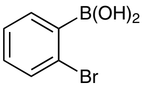
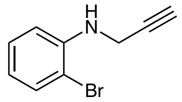
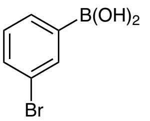
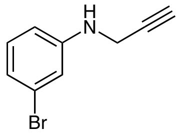
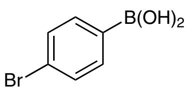
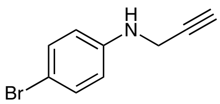
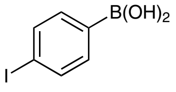
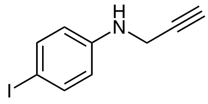
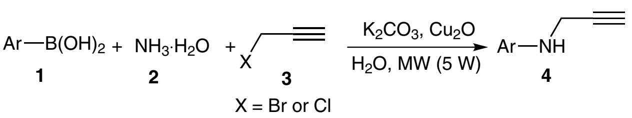
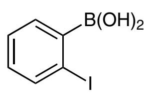
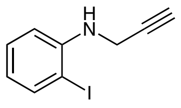
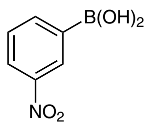
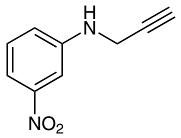
Entry	Boronic acid	Product	Yield (%)[b]	Yield (%)[c]
1	 **1a**	 **4a**	85	88
2	 **1b**	 **4b**	82	86
3	 **1c**	 **4c**	87	85
4	 **1d**	 **4d**	80	78
5	 **1e**	 **4e**	69	72
6	 **1f**	 **4f**	71	73
7	 **1g**	 **4g**	80	86
8	 **1h**	 **4h**	81	81
9	 **1i**	 **4i**	82	83

Table 2 Synthesis of Arylaminomethyl Acetylenes **4**[a] (continued)



Entry	Boronic acid	Product	Yield (%)[b]	Yield (%)[c]
10	 **1j**	 **4j**	69	76
11	 **1k**	 **4k**	70	66

[a] Reaction conditions: aromatic boronic acid **1** (0.5 mmol), NH_3 (**2**) (0.6 mmol, 25% aq solution), propargyl halide **3** (0.5 mmol), K_2CO_3 (138 mg, 1 mmol), H_2O (2 mL), MW (5 W), 10 min.[11]

[b] Yield of isolated product using propargyl bromide.

[c] Yield of isolated product using propargyl chloride.

In summary, we have reported a convenient and efficient microwave-assisted, three-component synthesis of arylaminomethyl acetylenes via the coupling of aromatic boronic acids, ammonia and propargyl halides (bromide or chloride), catalyzed by copper(I) oxide in water as the solvent. This method provides a rapid and low-energy consumption access to arylaminomethyl acetylenes, which are an important class of intermediates in medicinal, chemical, and materials science.

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(11) **Compounds 4; General Procedure**
To a microwave reaction tube were added aromatic boronic acid **1** (0.5 mmol), ammonia (**2**) (0.6 mmol, 25% aq solution), propargyl halide **3** (0.5 mmol), K_2CO_3 (138 mg, 1 mmol), and H_2O (2 mL). The reaction was conducted under microwave irradiation (5 W, CEM Discover-SP) for 10 min (with monitoring by TLC). After completion, the mixture

was diluted with H_2O (30 mL) and then extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with H_2O (3 × 10 mL) and brine (3 × 10 mL), and then dried over anhydrous Na_2SO_4. Evaporation of the solvent provided a crude residue, which was subjected to column chromatography over silica gel (EtOAc–PE, 1:8→1:3) to afford arylaminomethyl acetylene **4**.

4-Methyl-*N*-(prop-2-ynyl)aniline (4a)

Yield: 64 mg (88%); yellow oil. IR (KBr): 3397, 3289, 1616, 1519, 1482, 809 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.03$ (d, $J = 8.18$ Hz, 2 H), 6.62 (d, $J = 8.27$ Hz, 2 H), 3.91 (d, $J = 2.22$ Hz, 2 H), 3.73 (s, 1 H), 2.25 (s, 3 H), 2.20 (s, 1 H).[2a]

***N*-(Prop-2-ynyl)aniline (4b)**

Yield: 56 mg (86%); yellow oil. IR (KBr): 3405, 3288, 1505, 1440, 752 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.22$ (t, $J = 7.89$ Hz, 2 H), 6.79 (t, $J = 7.33$ Hz, 1 H), 6.69 (d, $J = 7.85$ Hz, 2 H), 3.94 (d, $J = 2.25$ Hz, 2 H), 3.87 (s, 1 H), 2.21 (s, 1 H).[1c]