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Original article

One-pot synthesis of *N*-aryl propargylamine from aromatic boronic acid, aqueous ammonia, and propargyl bromide under microwave-assisted conditions

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ABSTRACT

A facile, one-pot synthesis of *N*-aryl propargylamine from aromatic boronic acid, aqueous ammonia, and propargyl bromide has been achieved under microwave-assisted conditions. The reactions can be smoothly completed within a total 10 min through a two-step procedure, including copper-catalyzed coupling of aromatic boronic acids with aqueous ammonia and following propargylation by propargyl bromide.

1. Introduction

Terminal alkynes are widely used 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 to terminal alkynes are CBr_4/PPh_3, CCl_3CO_2H/TsCl, and the Bestmann–Ohira reagent and its analogs, in which superbases, such as BuLi, NaHMDS, and *t*-BuOK are usually employed at low temperatures [4]. Acid chlorides can be converted to 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 for this preparation, which undergo reduction, followed by a one-pot conversion to terminal alkynes [6]. Meanwhile, the dehydrobromination of 1- or 2-bromo-1-alkenes is a convenient method that has been developed in recent years [7]. In this procedure, both *trans*- and *cis*-configurations can be converted to terminal alkynes. The direct introduction of C≡CH residue into arenes and hetarenes through transition metal-catalyzed, cross-coupling reactions can generate the desired products. In this procedure, intermediate chemicals, such as acetylene, trimethylsilyl acetylene, propiolic acid, and ethynyltributyl stannane from suppliers, are often used [8]. In 2011, Huang found that the cleavage of 4-aryl-2-methyl-3-butyn-2-ols catalyzed by tetrabutylammonium hydroxide can produce terminal arylacetylenes [9]. This process is a rapid and efficient synthetic route, but the substrates are rare.

Enlightened by Fu's green synthesis of primary aromatic amines by coupling aromatic boronic acids with aqueous ammonia [10], we here report a convenient and efficient microwave-assisted (MW), two-step synthesis of *N*-aryl propargylamine **4** *via* the coupling of aromatic boronic acid **1** with ammonia **2**, and subsequent propargylation by propargyl bromide **3** in H_2O (Scheme 1) as a green solvent.

2. Experimental

All the reactions were conducted using CEM Discover-SP microwave instrument. ^1H NMR spectra were recorded using Bruker AM-500 and AM-400 spectrometer in $CDCl_3$ with $SiMe_4$ as

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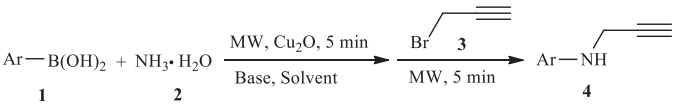

Scheme 1. One-pot synthesis of *N*-aryl propargylamine **4**.

an internal standard. IR spectra were performed on a Nexus FT-IR spectrophotometer. Commercially available reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF254 silica gel-coated plates. Column chromatography was carried out using 300–400 mesh silica gel at medium pressure.

General procedure for the synthesis of **4**: The microwave reaction tube was charged with boronic acid **1** (0.5 mmol), ammonia **2** (2 mmol, 25% aqueous solution), Cu_2O (8 mg, 0.05 mmol), and H_2O (2 mL). After the mixture was exposed to 5 W microwaves for 5 min, propargyl bromide **3** (59 mg, 0.5 mmol) was added. The mixture was then irradiated under 5 W microwaves for another 5 min. The system was diluted with 30 mL of H_2O after the reaction was completed, and the mixture was then extracted three times with EtOAc. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous Na_2SO_4. The evaporation of the solvent provided the crude product, which was subjected to column chromatography (silica gel, EtOAc-petroleum ether 1:8–1:3) to yield *N*-aryl propargylamine **4**.

4-Methyl-*N*-(prop-2-ynyl)aniline (**4a**) [11]: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (d, 2H, J = 8.18 Hz), 6.62 (d, 2H, J = 8.27 Hz), 3.91 (d, 2H, J = 2.22 Hz), 3.73 (s, 1H), 2.25 (s, 3H), 2.20 (s, 1H).

General procedure for the synthesis of **5**: The tube was charged with $AgSbF_6$ (17 mg, 0.05 mmol) after the propargylation process was completed. The mixture was irradiated by 5 W microwaves for 5 min. The system was diluted with 30 mL of H_2O after completion of the reaction, and the mixture was then extracted with EtOAc three times. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent provided the crude product, which was then subjected to column chromatography (silica gel, EtOAc-petroleum ether 1:5–1:2) to obtain the quinoline derivatives **5**.

6-Methylquinoline (**5a**) [12]: Light green oil; IR (KBr, cm^{-1}): 3398, 3014, 1594, 1501, 1373, 1119, 829; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (dd, 1H, J = 1.44, 4.12 Hz), 8.07 (d, 1H, J = 8.28 Hz), 8.00 (d, 1H, J = 8.6 Hz), 7.58 (m, 1H), 7.55 (dd, 1H, J = 1.88, 8.6 Hz), 7.37 (dd, 1H, J = 4.24, 8.28 Hz), 2.54 (s, 3H).

3. Results and discussion

The reaction of *p*-tolylboronic acid **1a** (0.5 mmol), ammonia **2** (25% aqueous solution), propargyl bromide **3** (0.5 mmol), base (1 mmol), Cu_2O, and 2 mL of solvent under microwave-assisted conditions was chosen as the model reaction for the preparation of the *N*-monopropargylated product, 4-methyl-*N*-(prop-2-ynyl)-aniline **4a**, in which 5 min were allocated respectively in each step (Table 1).

The realized yield of the product **4a** was only 32% when the system was heated to 70 °C for 3 h in each step without MW energy (Table 1, entry 1), but increased to 61% when a microwave power of 5 W was used (entry 2). The reaction favored polar solvents, such as DMSO, DMF, and H_2O, and satisfactory yields were observed (entries 2 and 5–16), whereas no product was detected when DCE, or PhMe, was used as the solvent (entries 3 and 4). The reaction can work smoothly in H_2O, generating an excellent yield of 87% when 4 equiv. of ammonia and 0.1 equiv. of Cu_2O were used (entry 7). A higher or lower loading of ammonia or Cu_2O will decrease the yield (entries 8, 9, 15, and 16). The base, K_2CO_3, is more efficient than others, such as Cs_2CO_3, KOAc, and Et_3N in this reaction (entries 11–14). A microwave power of 5 W was better than a lower, or higher, one (entries 7, 10, and 11). The reaction proceeded more efficiently when promoted by a microwave power of 5 W in 2 mL of H_2O for 5 min in each step respectively using *p*-tolylboronic acid **1a** (0.5 mmol), ammonia **2** (4 equiv.), propargyl bromide **3** (0.5 mmol), Cu_2O (0.1 equiv.), and K_2CO_3 as the base. The product, 4-methyl-*N*-(prop-2-ynyl)aniline **4a**, was isolated with 87% yield when this optimum reaction condition was used (entry 7).

A series of aromatic boronic acid **1** were then subjected to this reaction under optimized reaction conditions. All the reactions were completed within the total 10 min, and moderate to excellent yields of *N*-aryl propargylamine **4** were achieved, as shown in Table 2. The reaction of aromatic boronic acids containing electron-donating groups, such as methyl and methoxyl, proceeded with higher yields (Table 2, **4a** and **4c**) compared to anilines containing electron-withdrawing groups, such as nitryl, bromo, chloro, and iodo (Table 2, **4d**–**4k**). Notably, aromatic boronic acids containing either, an electron-donating, or an electron-withdrawing group at the *para* position can provide excellent yields (Table 2, **4a**, **4c**, **4d**, **4h**, and **4i**). Although the substrates containing the *o*-substituent provided lower yields, the reactions can also be completed smoothly within total 10 min (Table 2, **4f** and **4j**).

Moreover, this procedure can be used as a facile method for the synthesis of potential bioactive quinoline derivatives through a

Table 1
Optimization of the synthesis to 4-methyl-*N*-(prop-2-ynyl)aniline **4a**.

Entry	Solvent	Equiv. of $NH_3{\cdot}H_2O$	Base	Equiv. of Cu_2O	MW (W)	Yield of **4a**[a]
1[b]	DMSO	2	K_2CO_3	0.1	70 °C	32%
2	DMSO	2	K_2CO_3	0.1	5	61%
3[c]	DCE	2	K_2CO_3	0.1	5	N.R.
4[c]	PhMe	2	K_2CO_3	0.1	5	N.R.
5	DMF	2	K_2CO_3	0.1	5	60%
6	H_2O	2	K_2CO_3	0.1	5	81%
7	H_2O	4	K_2CO_3	0.1	5	87%
8	H_2O	3	K_2CO_3	0.1	5	80%
9	H_2O	5	K_2CO_3	0.1	5	82%
10	H_2O	4	K_2CO_3	0.1	8	75%
11	H_2O	4	K_2CO_3	0.1	3	79%
12	H_2O	4	Cs_2CO_3	0.1	5	75%
13	H_2O	4	KOAc	0.1	5	45%
14	H_2O	4	Et_3N	0.1	5	23%
15	H_2O	4	K_2CO_3	0.05	5	78%
16	H_2O	4	K_2CO_3	0.2	5	63%

[a] Isolated yields.
[b] This reaction was conducted by heating to 70 °C without microwave.
[c] The reaction did not work.