Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 5597

Received 22nd May 2014,
Accepted 13th June 2014

DOI: 10.1039/c4ob01055h

www.rsc.org/obc

Synthesis of tertiary propargylamines *via* a rationally designed multicomponent reaction of primary amines, formaldehyde, arylboronic acids and alkynes†

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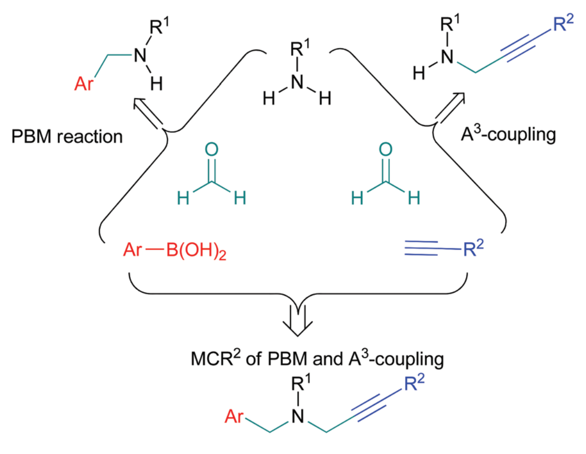
A novel approach for the synthesis of tertiary propargylamines is achieved through a $Cu(OAc)_2$-catalyzed multicomponent reaction of primary amines, formaldehyde, arylboronic acids and alkynes, where a combination of PBM and A^3-coupling reactions is involved in this new multicomponent reaction.

Multicomponent reactions (MCR), generally with high selectivity, flexibility and atom economy, are among the most powerful synthetic strategies to access diverse complex structures from small molecular compounds,[1] and a variety of new MCRs have been developed.[2,3] Among them, the combination of MCR (MCR^2), which combines two different types of MCRs in a single process, has gained considerable attention.[4] However, the Ugi reaction as well as isonitriles are indispensably involved in most of the MCR^2 cases.[2a,c,4] Therefore, the development of novel MCR^2 without the Ugi reaction is highly valuable.

The three-component reaction of aldehydes, amines and alkynes (A^3-coupling) provides an efficient strategy to the synthesis of propargylamines, which are often useful key intermediates and building blocks for the preparation of many biologically active compounds.[5,6] A number of metal catalysts, such as Au salts,[7a] Ag salts,[7b] $FeCl_3/Fe_2O_3/Fe_3O_4$,[7c,d] $InCl_3$,[7e] Cu salts,[7f,i] and so on,[5,6b] have been applied for this reaction *via* C–H activation of terminal alkynes. Meanwhile, the Petasis borono–Mannich (PBM) reaction of aldehydes, amines and boronic acids, developed by Petasis in 1993,[8] has attracted considerable attention in the synthesis of diverse α-hydroxyl amines, α-amino acids and nitrogen-containing heterocycles.[9,10] Realizing both amines and aldehydes are involved in A^3-coupling and PBM reactions, and a secondary amine is generally preferable to a primary one in A^3 reaction;[5,7] it is possible to develop a novel multicomponent reaction in which the secondary amines produced from PBM reaction could serve as the amine component in further A^3-coupling to construct the final propargylamines. Thus, a novel five-component MCR^2 of PBM and A^3-coupling reactions has been accomplished and reported herein (Scheme 1).

At the outset, CuI was chosen as the catalyst to screen the effect of solvents on the model reaction of aniline, formaldehyde, phenylboronic acid and phenylacetylene at 80 °C for 24 h. The nature of the solvent significantly affected the reaction (Table 1). Among the solvents screened, 1,2-dichloroethane (DCE) was found to be the most suitable solvent for the combination of PBM and A^3-coupling reactions with a desired product yield of 86% (Table 1, entry 1). Toluene was inferior and generated the corresponding product in 72% yield (Table 1, entry 2), whereas acetonitrile and 1,4-dioxane afforded lower yields of the desired products (Table 1, entries 3 and 4). Tetrahydrofuran (THF), ethanol and water delivered less than 5% yield (Table 1, entries 5–7), and no desired product was achieved when the reactions were performed in *N*,*N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) (Table 1, entries 8 and 9). When the reaction was performed in the absence of a solvent, a lower yield of 22% was obtained



Scheme 1 A combination of PBM and A^3-coupling reactions.

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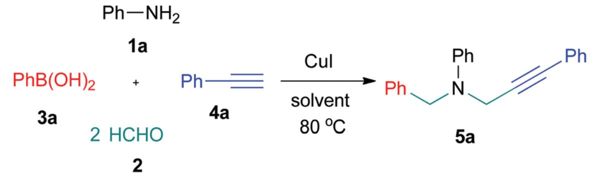
† Electronic supplementary information (ESI) available: Experimental section, spectroscopic data. See DOI: 10.1039/c4ob01055h

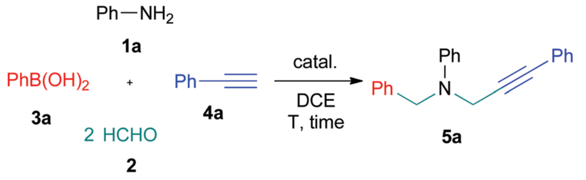
Table 1 Effect of solvent for the five-component reaction[a]



Entry	Solvent	Yield[b] (%)
1	DCE	86
2	Toluene	72
3	1,4-Dioxane	12
4	MeCN	32
5	THF	<5
6	EtOH	<5
7	H_2O	<5
8	DMF	0
9	DMSO	0
10	Neat	22
11	DCE	0[c]

[a] Reaction conditions: aniline (1 mmol), formaldehyde (40% aqueous solution) (2.2 mmol), phenylboronic acid (1.05 mmol), phenylacetylene (1.2 mmol), CuI (10 mol%), solvent (3 mL), 80 °C, 24 h. [b] Yields were determined by GC using an internal standard. [c] Without catalyst.

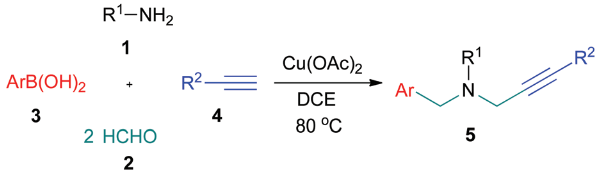
Table 2 Catalyst and conditions screening for the five-component reaction[a]

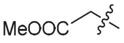
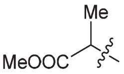


Entry	Catalyst	Temp. (°C)	Time (h)	Yield[b] (%)
1	CuI	80	24	86
2	CuBr	80	24	89
3	CuCl	80	24	71
4	CuOAc	80	24	89
5	Cu_2O	80	24	68
6	**$Cu(OAc)_2$**	**80**	**24**	**96**
7	$CuBr_2$	80	24	46
8	$CuCl_2$	80	24	51
9	$CuSO_4$	80	24	68
10	CuO	80	24	54
11	Cu	80	24	65
12	$Cu(CF_3SO_3)_2$	80	24	32
13	$Cu(OAc)_2$	25	24	<5
14	$Cu(OAc)_2$	60	24	72
15	$Cu(OAc)_2$	80	24	62[c]
16	$Cu(OAc)_2$	80	12	71

[a] Reaction conditions: aniline (1 mmol), formaldehyde (40% aqueous solution) (2.2 mmol), phenylboronic acid (1.05 mmol), phenylacetylene (1.2 mmol), catalyst (10 mol%), DCE (3 mL) at a temperature indicated in the table, 12–24 h. [b] Yields were determined by GC using an internal standard. [c] 5 mol% of $Cu(OAc)_2$ was used.

Table 3 Substrate scope and limitations[a]



Entry	R^1	Ar	R^2	Yield[b] (%)
1	Ph	Ph	Ph	92
2	*p*-(MeO)–Ph	Ph	Ph	91
3	*p*-Me–Ph	Ph	Ph	78
4	*p*-Cl–Ph	Ph	Ph	60
5	*p*-F–Ph	Ph	Ph	66
6	*o*-Me–Ph	Ph	Ph	74
7	*m*-Me–Ph	Ph	Ph	86
8	*p*-NO_2–Ph	Ph	Ph	0
9	Bn	Ph	Ph	90
10	*n*-Butyl	Ph	Ph	71[c]
11	 MeOOC	Ph	Ph	64[c]
12	 Me MeOOC	Ph	Ph	60[c]
13	Ph	*p*-(MeO)–Ph	Ph	95
14	Ph	*p*-Me–Ph	Ph	87
15	Ph	*p*-Cl–Ph	Ph	61
16	Ph	*p*-F–Ph	Ph	60
17	Ph	*o*-(MeO)–Ph	Ph	79
18	Ph	*p*-CF_3–Ph	Ph	0
19	*p*-(MeO)–Ph	*p*-(MeO)–Ph	Ph	86[c]
20	Ph	Ph	*p*-Me–Ph	82
21	Ph	*p*-Cl–Ph	*p*-Me–Ph	61[c]
22	*p*-(MeO)–Ph	*p*-(MeO)–Ph	*p*-Me–Ph	82
23	Ph	Ph	*p*-Cl–Ph	70
24	Ph	Ph	*n*-Butyl	82[c]
25	Ph	Ph	*n*-Pentyl	78[c]
26	Ph	Ph	MeOOC–	40[c]

[a] A mixture of aniline **1** (1 mmol), formaldehyde **2** (40% aqueous solution) (2.2 mmol), arylboronic acid **3** (1.05 mmol), alkyne **4** (1.2 mmol), $Cu(OAc)_2$ (10 mol%) and DCE (3 mL) was stirred at 80 °C for 24 h. [b] Isolated yields. [c] The reaction time is 48 h.

(Table 1, entry 10), and no desired product was detected without the catalyst (Table 1, entry 11).

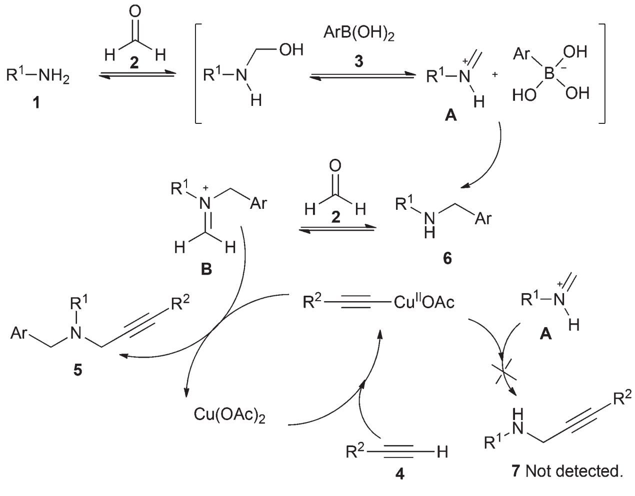
We next investigated the catalytic activity of various copper salts (Table 2). $Cu(OAc)_2$ was found to be the most effective catalyst with a high yield of 96% (Table 2, entry 6). Interestingly, except for CuOAc/$Cu(OAc)_2$, Cu(I) catalysts showed better catalytic activities than Cu(II) catalysts (Table 2, entries 1–12). $Cu(OAc)_2$ was therefore adopted for the optimization of other reaction conditions. As to the temperature, 80 °C was found to be optimal. The reactions at lower temperatures generated less product (Table 2, entries 13 and 14). Lowering the catalyst load amount to 5 mol%, or reducing the reaction time to 12 h also resulted in decrease of yield (Table 2, entries 15 and 16).

On the basis of the optimized reaction conditions (Table 2, entry 6), the scope of this five-component reaction was evaluated (Table 3). In general, for all components in this reaction, electron-donating substituents (–MeO and –Me) on the phenyl ring lead to higher yields than electron-withdrawing groups (–Cl and –F) (Table 3, entries 1–7, 13–17 and 19–23). The reaction almost ceased when a reactant with a highly electron deficient substituent, such as 4-nitroaniline or

4-(trifluoromethyl)phenylboronic acid was adopted (Table 3, entries 8 and 18). For the amine component, substituted anilines delivered the corresponding products in 60–92% yields (Table 3, entries 1–7). Aliphatic amines, such as phenylmethanamine and butan-1-amine, also delivered desired products in satisfactory yields (Table 3, entries 9 and 10). Furthermore, the successful application of methyl 2-aminoacetate and methyl 2-aminopropanoate in this MCR^2 (Table 3, entries 11 and 12) might provide a complementary approach to the functionalization of NH_2-terminal amino acid esters or peptides.[7h,i] As for the alkyne component, in addition to the success of phenylacetylenes (Table 3, entries 1–7, 9–17 and 19–23), aliphatic alkynes also worked smoothly and desired products were obtained in moderate yields with prolonged reaction time of 48 h (Table 3, entries 24–26).

A tentative mechanism for this five-component reaction is proposed in Scheme 2. The reaction of primary amine **1**, formaldehyde **2**, and arylboronic acid **3** afforded a secondary amine **6** *via* the PBM reaction,[8,9,11] which was detected by GC-MS throughout the reaction. The secondary amine **6** might further react with formaldehyde **2** to produce an iminium intermediate **B**. The copper acetylide intermediate, generated from alkyne **4** and $Cu(OAc)_2$, reacted with iminium **B** to give the corresponding propargylamine **5** and regenerated the copper catalyst for further reactions.[5,7] Thus, this five-component reaction involved a MCR^2 of PBM and A^3-coupling reactions.

In conclusion, we have developed a novel approach to the synthesis of tertiary propargylamines *via* a rationally designed Cu-catalyzed multicomponent reaction of primary amines, formaldehydes, arylboronic acids and alkynes. The combination of PBM and A^3-coupling reactions provides an efficient and fast one-pot approach to the tertiary propargylamines. Both aromatic and aliphatic amines and alkynes are applicable. Furthermore, the MCR^2 also provided a complementary pathway to the functionalization of NH_2-terminal amino acid esters and peptides.



Scheme 2 Proposed reaction mechanism.

Financial support for this work from the National Basic Research Program of China (973 program) (grant no. 2010CB126101), the National Natural Science Foundation of China (grant 20972052) and the Shanghai Key Laboratory of Catalysis Technology for Polyolefins (LCTP-201301) are gratefully acknowledged.

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