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PII: S0040-4039(14)02231-X
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.12.142
Reference: TETL 45667

To appear in: *Tetrahedron Letters*

Received Date: 23 November 2014
Revised Date: 22 December 2014
Accepted Date: 29 December 2014

Please cite this article as: Wang, J., Shen, Q., Zhang, J., Song, G., Metal-free multicomponent coupling reaction of aliphatic amines, formaldehyde, oganoboronic acids and propiolic acids for the synthesis of diverse propargylamines, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2014.12.142

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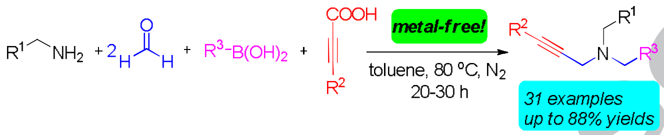

Tetrahedron Letters
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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

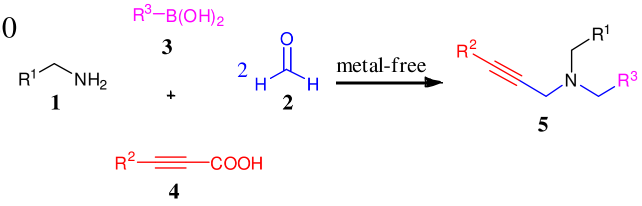
Keywords:
Multicomponent reaction
Metal-free
Propargylamines
Petasis-borono Mannich reaction
Decarboxylative coupling

ABSTRACT

A metal-free multicomponent coupling reaction of aliphatic amines, formaldehyde, oganoboronic acids and propiolic acids has been reported for the synthesis of diverse propargylamines. This transformation involves a MCR^2 of PBM and decarboxylative three-component coupling reactions.

Propargylamines are important intermediates and skeletons for the preparation of diverse heterocyclic compounds, such as pyrroles,[1] pyrrolidines,[2] pyrrolophanes,[3] aminoindolizines,[4] isoindoline,[5] imidazolidinones,[6] 2-aminoimidazoles[7] and oxazolidinones.[8] Among variety strategies for the synthesis of propargylamines, the three-component coupling reaction of an aldehyde, an amine and an alkyne (A^3-coupling) has been recognized as the most efficient and powerful method.[9-10] However, transition metal catalysts are necessary in A^3-coupling to generate metal acetylide intermediate to fulfill the reaction. Lee and coworkers[11] reported the synthesis of propargylamines via a metal-free decarboxylative three-component reaction of propiolic acids,[12] paraformaldehyde and secondary amines. The replacement of alkynes with propiolic acids in their reported reaction can lead to easily generation of carbon nucleophile for further attacking the iminium salt, avoiding the use of metal catalysts. However, only secondary amines were adoptable in this reaction restricting its application. Therefore, it is of high demand to develop a more applicable metal-free strategy for the synthesis of propargylamines.

The combination of multicomponent reactions (MCR^2),[13] which combines different types of MCRs in one pot process inheriting the high selectivity, efficiency and atom economy of MCR, has gained more and more attentions, since Dömling and Ugi reported the first MCR^2 of a modified Asinger four-component reaction (4CR) and the Ugi 4CR.[14] However, most of the reported MCR^2 cases are limited in isonitrile based multicomponent reactions.[15] Recently, we developed a combination of Petasis borono-Mannich (PBM) [16-17] and A^3-coupling reactions, where the secondary amines produced from PBM reaction participated in further A^3-coupling affording the final propargylamines.[18] However, a catalytic amount of $Cu(OAc)_2$ was needed. As our interest in the development of novel MCR^2 and metal-free MCR,[19] we reported herein a metal-free multicomponent reaction of amines, formaldehyde, organoboronic acids and propiolic acids for the direct synthesis of diverse propargylamines (Scheme 1).



Scheme 1 Metal-free synthesis of propargylamines.

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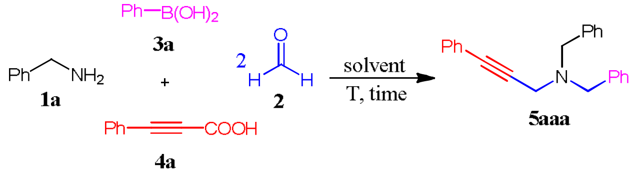
Table 1 Optimization of conditions for the synthesis of propargylamine.[a]



Entry	1a/2/3a/4a (ratio)	T/°C	time/h	solvent	Yield[b]/%
1	1.0/2.5/1.2/1.2	80	20	toluene	81
2	1.0/2.5/1.2/1.2	80	20	xylene	61
3	1.0/2.5/1.2/1.2	80	20	DCE	64
4	1.0/2.5/1.2/1.2	80	20	THF	6
5	1.0/2.5/1.2/1.2	80	20	dioxane	<5
6	1.0/2.5/1.2/1.2	80	20	MeCN	<5
7	1.0/2.5/1.2/1.2	80	20	water	<5
8	1.0/2.5/1.2/1.2	80	20	EtOH	nd
9	1.0/2.5/1.2/1.2	80	20	DMF	nd
10	1.0/2.5/1.2/1.2	80	20	DMSO	nd
11	1.0/2.5/1.1/1.2	80	20	toluene	68
12	1.0/2.5/1.4/1.2	80	20	toluene	84
13	1.0/2.5/1.5/1.2	80	20	toluene	89
14	1.0/2.5/1.6/1.2	80	20	toluene	88
15	1.0/2.5/1.5/1.1	80	20	toluene	85
16	**1.0/2.5/1.5/1.3**	**80**	**20**	**toluene**	**94 (87)**
17	1.0/2.5/1.5/1.4	80	20	toluene	87
18	1.0/2.5/1.5/1.3	80	20	toluene	78
19	1.0/2.5/1.5/1.3	80	20	toluene	82
20	1.0/2.5/1.5/1.3	25	20	toluene	75
21	1.0/2.5/1.5/1.3	60	20	toluene	78
22	1.0/2.5/1.5/1.3	100	20	toluene	82
23	1.0/2.5/1.5/1.3	80	20	toluene	84
24	1.0/2.5/1.5/1.3	80	20	toluene	<5[c] + 45[c,d]

The bold values are the most effective conditions for the model reaction.

[a] All reactions were performed on a 1.0 mmol-scale with 2.5 mL solvent under a nitrogen atmosphere. Formaldehyde aqueous solution (40%) was used. nd = not detected.

[b] Yields were determined by GC using an internal standard. Isolated yield was given in parentheses.

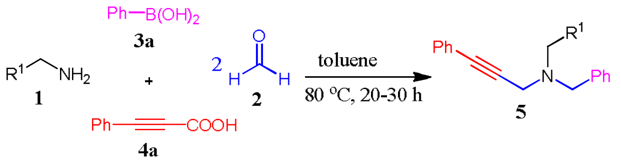
[c] Under air atmosphere.

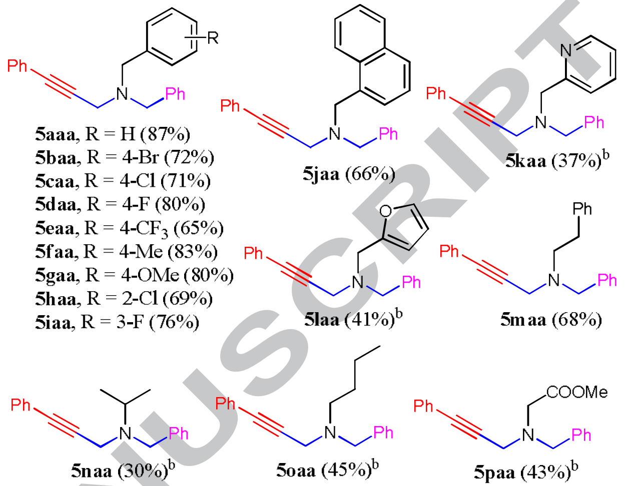
[d] Isolated yield of *N*-benzyl-*N*-methyl-3-phenylpropargylamine.

The optimization of reaction conditions were initially performed on the model reaction of phenylmethanamine (**1a**), formaldehyde (**2**), phenylboronic acid (**3a**) and phenylpropiolic acid (**4a**) with a ratio of 1.0:2.5:1.2:1.2. Toluene was found to be the most suitable solvent for the multicomponent reaction with a desired product yield of 81% (Table 1, entry 1), while xylene and 1,2-dichloroethane (DCE) were less effective and afforded the product in 61% and 64% yields, respectively (Table 1, entries 2-3). Replacement of toluene with other solvents, such as tetrahydrofuran (THF), dioxane, acetonitrile, water, ethanol, *N*,*N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO), either delivered quite low yields (Table 1, entries 4-7) or gave no products (Table 1, entries 8-10). Investigation on the ratio of reactants indicated that a 1.0:2.5:1.5:1.3 ratio of **1a/2/3a/4a** gave the best result with an isolated yield of 87% (Table 1, entries 11-19). Further screening of the reaction conditions revealed that decreasing the temperature down to 60 or 25 °C (Table 1, entries 20-21) or elevating up to 100 °C (Table 1, entriy 22) or increasing the reaction time to 30 h (Table 1, entry 23) did not promote the reaction yields. While the reaction was conducted under air atmosphere, less than 5% yield of desired product was detected, and 45% yield of *N*-benzyl-*N*-methyl-3-phenylpropargylamine was obtained as the main byproduct (Table 1, entry 24).[20]

With the reaction conditions in entry 16 of Table 1, we began to explore the scope of the multicomponent reaction. First, various primary amines were subjected to the reaction with **2**, **3a** and **4a** (Table 2). In general, phenylmethanamine bearing *para*-, *ortho*- and *meta*-substituents such as fluoro, chloro, bromo, trifluoromethyl, methyl, methoxyl groups on the benzene ring participated in the reaction to afford the desired products **5aaa**-**5iaa** in moderate to good yields. Naphthalen-1-ylmethanamine and 2-phenylethanamine also produced their corresponding products **5jaa** and **5maa** in 66% and 68% yields, respectively. Derivation from the phenyl substituent to aromatic heterocycles such as pyridinyl and furanyl decreased the yield (**5kaa** and **5laa**). Other simple aliphatic amines such as propan-2-amine, butan-1-

Table 2 Reaction of various primary amines with formaldehyde, phenylboronic acid and phenylpropiolic acid.[a]



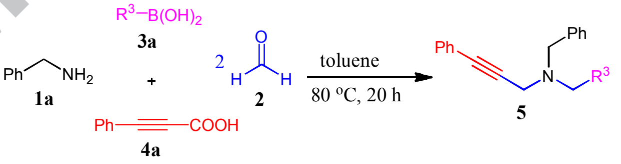


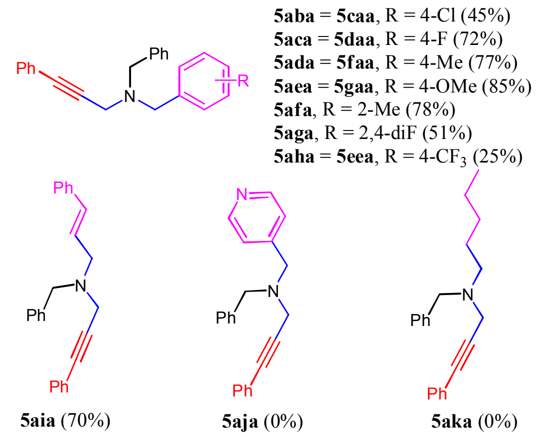
5aaa, R = H (87%)
5baa, R = 4-Br (72%)
5caa, R = 4-Cl (71%)
5daa, R = 4-F (80%)
5eaa, R = 4-CF_3 (65%)
5faa, R = 4-Me (83%)
5gaa, R = 4-OMe (80%)
5haa, R = 2-Cl (69%)
5iaa, R = 3-F (76%)
5jaa (66%)
5kaa (37%)[b]
5laa (41%)[b]
5maa (68%)
5naa (30%)[b]
5oaa (45%)[b]
5paa (43%)[b]

[a] The reaction conditions were the same as entry 16 in Table 1. Isolated yields were given in parentheses.

[b] The reaction time is 30 h.

Table 3 Reaction of various arylboronic acids with phenylmethanamine, formaldehyde and phenylpropiolic acid.[a]



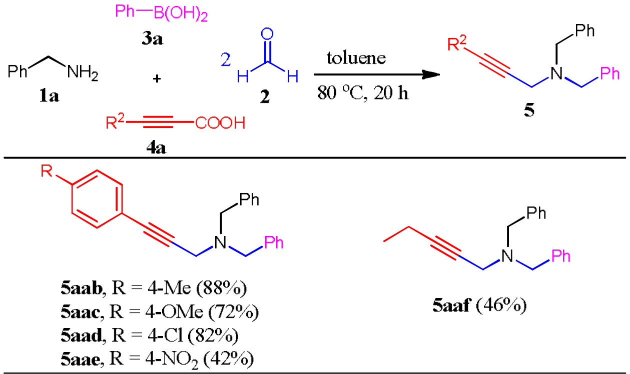


5aba = **5caa**, R = 4-Cl (45%)
5aca = **5daa**, R = 4-F (72%)
5ada = **5faa**, R = 4-Me (77%)
5aea = **5gaa**, R = 4-OMe (85%)
5afa, R = 2-Me (78%)
5aga, R = 2,4-diF (51%)
5aha = **5eea**, R = 4-CF_3 (25%)
5aia (70%)
5aja (0%)
5aka (0%)

[a] The reaction conditions were the same as entry 16 in Table 1. Isolated yields were given in parentheses.

amine and methyl 2-aminoacetate, were also applicable with lower yields (**5naa**, **5oaa** and **5paa**).

Table 4 Reaction of various propiolic acids with phenylmethanamine, formaldehyde and phenylboronic acid.[a]

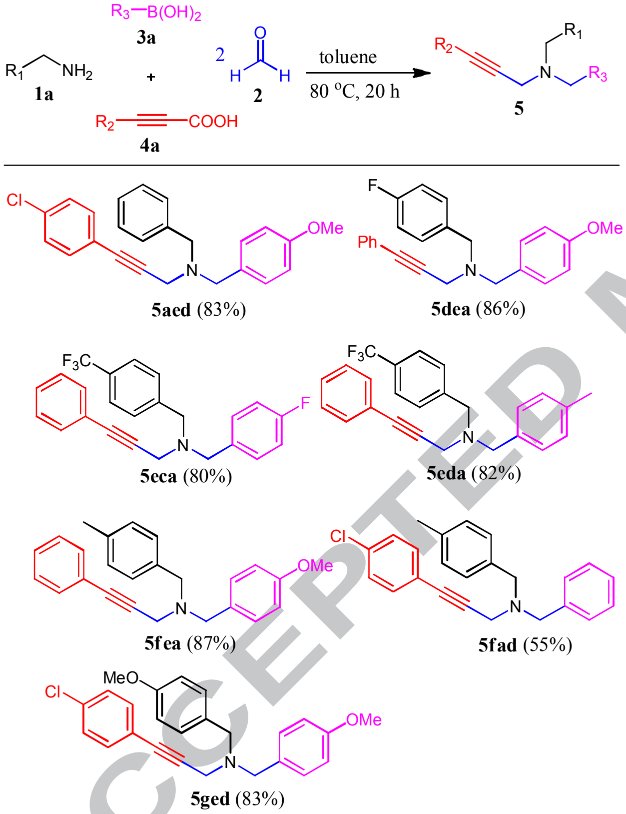


5aab, R = 4-Me (88%)
5aac, R = 4-OMe (72%)
5aad, R = 4-Cl (82%)
5aae, R = 4-NO$_2$ (42%)

5aaf (46%)

[a] The reaction conditions were the same as entry 16 in Table 1. Isolated yields were given in parentheses.

Table 5 Synthesis of diverse propargylamines.[a]



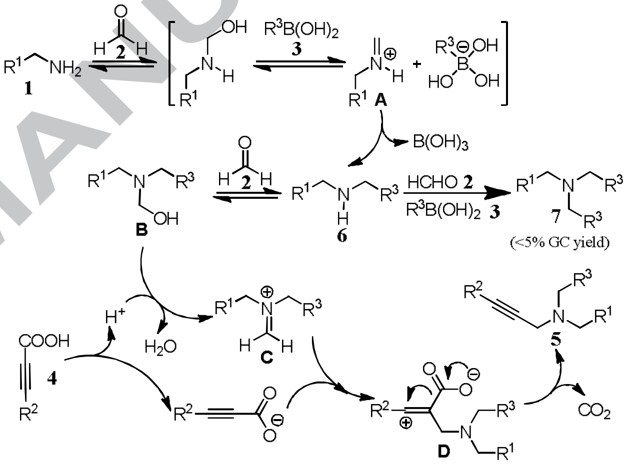
5aed (83%)
5dea (86%)
5eca (80%)
5eda (82%)
5fea (87%)
5fad (55%)
5ged (83%)

[a] The reaction conditions were the same as entry 16 in Table 1. Isolated yields were given in parentheses.

Next, the reaction of phenylmethanamine (**1a**), formaldehyde (**2**), phenylpropiolic acid (**4a**) and various organoboronic acids was examined (Table 3). Generally, electron-donating substituents (–OMe and –Me) on the phenyl ring of arylboronic acids resulted in higher yields than electron-withdrawing groups (–Cl and –F) (see **5aba**-**5aga**). While a highly electron withdrawing group on the phenyl ring led to a dramatic decrease in product yield (see **5aha**). Furthermore, the use of (*E*)-styrylboronic acid delivered corresponding 1,6-enyne product (**5aia**) with 70% yield. Unfortunately, aromatic heterocycle and aliphatic boronic acids shut down the reaction (see **5aja** and **5aka**).

Subsequently, the scope of propiolic acids was then investigated (Table 4). A nitro group on the phenyl ring or an aliphatic propiolic acid delivered the desired products (**5aae** and **5aaf**) with lower yields. However, both arylpropiolic acids and aliphatic propiolic acid were applicable in the multicomponent reaction in satisfactory yields (**5aab**-**5aaf**). Finally, the munticomponent coupling reaction of amines, formaldehyde, organoboronic acids and propiolic acids was applied for the synthesis of diverse propargylamines (Table 5).

A tentative mechanism for the metal-free, five-component reaction is proposed in Scheme 2. The reaction of primary amine **1**, formaldehyde **2**, and organoboronic acid **3** afforded a secondary amine **6** *via* the PBM reaction,[16] which could undergo a second PBM reaction with formaldehyde **2** and organoboronic acid **3** to produce the byproduct **7** as detected by GC-MS.[19a] The reaction of the secondary amine **6** and formaldehyde **2** generated hemiaminal **B**. The proton from propiolic acid **4** accelerated the formation of iminium salt **C**, which was further attacked by the alkynyl carbon bonded to carboxylate to form intermediate **D**. And the final desired propargylamine was generated through decarboxylation of **D**.[11,21] Thus, a MCR^2 of PBM and decarboxylative three-component coupling reactions was involved in this new five-component reaction.



Scheme 2 Proposed mechanism.

In conclusion, we have successfully developed a novel approach for the synthesis of propargylamines through a metal-free five-component coupling reaction of aliphatic amines, formaldehyde, oganoboronic acids and propiolic acids. The starting material is easily available. Both aromatic and aliphatic alkynyl carboxylic acids are applicable in this approach. Notably, this protocol avoids the use of any metal catalysts making this method more environmentally benign. Further studies on the synthetic applications are ongoing in our laboratory.

Acknowledgments

The financial support for this work from the National Key Technology R&D Program (Grant No. 2011BAE06B05-4) and Shanghai Key Laboratory of Catalysis Technology for Polyolefins (LCTP-201301) are gratefully acknowledged.

Supplementary Material

Experimental procedures, characterization data of products, and copies of ^{1}H and ^{13}C NMR can be found, in the online version, at http://....

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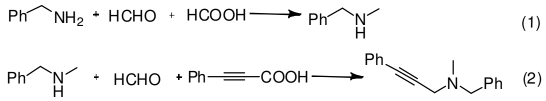
20. It was speculated that reaction under air atmosphere led to partial oxidation of formaldehyde to formic acid. Reduction of imine generated from benzylamine and formaldehyde by formic acid produced *N*-methyl-1-phenylmethanamine [Eq. (1)].[21] Further decarboxylative three-component coupling of *N*-methyl-1-phenylmethanamine, formaldehyde and phenylpropiolic acid delivered the undesired product *N*-benzyl-*N*-methyl-3-phenyl propargylamine [Eq. (2)].[11]



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