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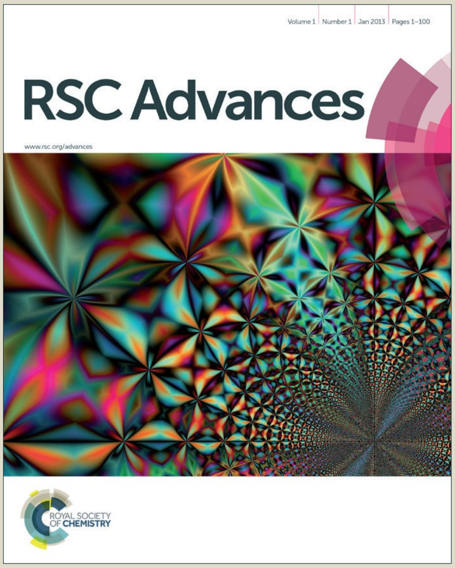

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Facile and Diverse Microwave-Assisted Synthesis of Secondary Propargylamines in Water Using CuCl/$CuCl_2$

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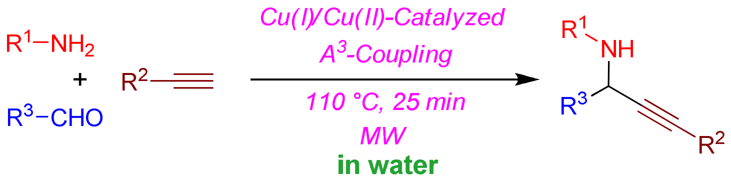
Abstract: A highly efficient microwave-assisted three-component reaction between an aldehyde, a primary amine and an alkyne was developed using an inexpensive Cu(I)/Cu(II) catalytic system and water as solvent. A wide range of diversely substituted secondary propargylamines was prepared in good and high yields within a short period of time.

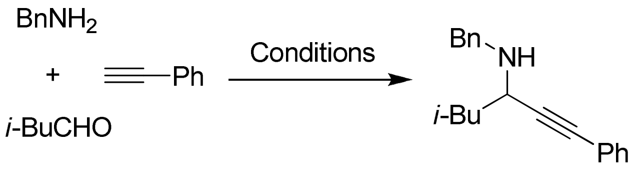


Introduction

Multicomponent reactions (MCRs) have attracted much attention in the framework of combinatorial and green chemistry owing to their synthetic efficiency and procedural simplicity.[1] These reactions constitute a valuable tool for the creation of large libraries of structurally related, drug-like compounds, thereby enabling rapid lead identification and lead optimization in drug discovery. MCRs provide a viable synthetic strategy to access complex structures from rather simple starting materials *via* a one-pot methodology, and in particular, exhibit high atom economy and selectivity.[2] A typical example of such a process is a three-component coupling of an aldehyde, an amine and an alkyne (A^3-coupling) affording propargylamines.[3-5] Secondary propargylamines are generally used in organic synthesis as precursors and versatile building blocks for the preparation of nitrogen-containing heterocyclic compounds such as pyrrolidines,[6] pyrroles,[7] oxazolidinones,[8] aminoindolizines[9] and 2-aminoimidazoles[10] and also act as key intermediates[11] for the construction of biologically active compounds like isosteres, β-lactams, oxotremorine substrates, conformationally restricted peptides, and therapeutic drug molecules.[12] However, there are only few direct approaches to secondary propargylamines via classical A^3-coupling. Considerable progress in the synthesis of secondary propargylamines has been made using ionic liquids[13] and microwave irradiation[14] in the presence of copper(I) catalysts. Very recently the synthesis of secondary propargylamines was reported via a three-component coupling of a ketone, a primary amine and an alkyne (KA^2-coupling) in the presence of copper(I) or copper(II) catalysts.[15] However, to the best of our knowledge, there is only one example of secondary propargylamines prepared in a domestic microwave oven in water as solvent.[16,17] Therefore, we wish to report here a simple but effective procedure for the microwave-assisted three-component reaction between an aldehyde, a primary amine and an alkyne using a Cu(I)/Cu(II) catalytic system and water as solvent.

We started our initial investigations applying the recently reported reaction conditions[14] for microwave-assisted A^3-coupling using 20 mol% of CuBr in water (Table 1, entry 1). However, the desired propargylamine was obtained only in 57% yield. Similarly, other copper(I) and silver(I) sources afforded the product in moderate yields (Table 1, entries 2-4). Remarkably, at the same temperature copper(II) salts provided the target product in higher yields (Table 1, entries 5,6). When we tried the combination of copper(I) and copper(II) chlorides the corresponding propargylamine was obtained in 83% yield (Table 1, entry 7). Finally, after increasing the temperature of the reaction to 110 °C, we obtained the product in 96% yield (Table 1, entry 8). Shortening the reaction time and lowering the catalysts loading resulted in decreased yields (Table 1, entries 9, 10).

Table 1. Optimization of the Reaction Parameters[a]

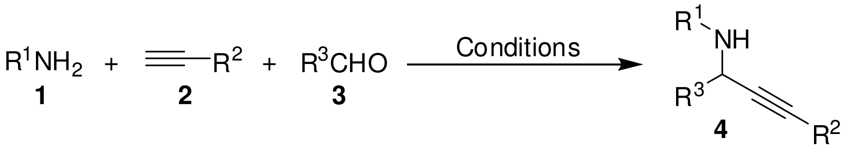


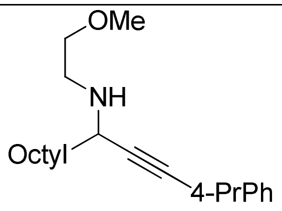
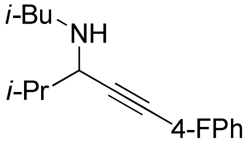
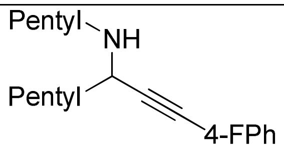
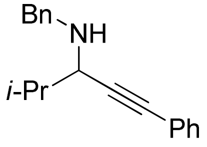
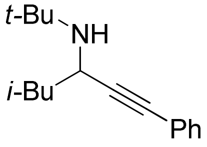
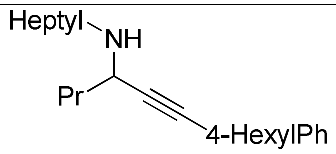
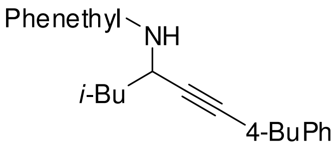
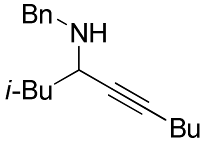
Entry	Catalyst (mol%)	Temp. (°C)	Time (min)	Yield (%)[b]
1	CuBr (20)	100	25	57
2	CuCl (20)	100	25	54
3	CuI (20)	100	25	58
4	AgOTf (20)	100	25	51
5	$Cu(OTf)_2$ (20)	100	25	69
6	$CuCl_2$ (20)	100	25	74
7	CuCl (10) + $CuCl_2$ (10)	100	25	83
8	**CuCl (10) + $CuCl_2$ (10)**	**110**	**25**	**96**
9	CuCl (10) + $CuCl_2$ (10)	110	10	71
10	CuCl (5) + $CuCl_2$ (5)	110	25	87

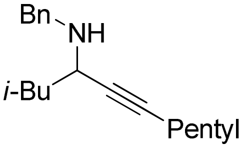
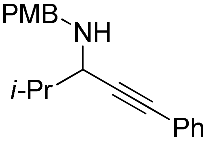
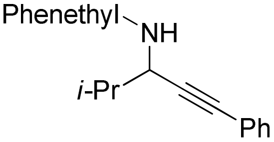
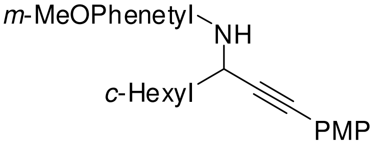
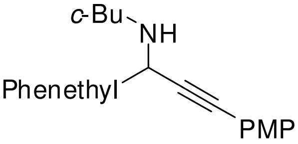
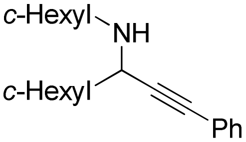
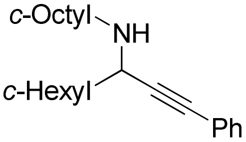
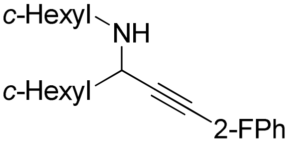
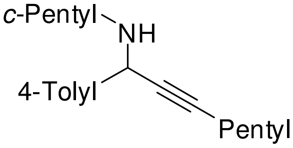
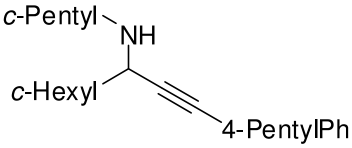
[a] Molar ratio: aldehyde/amine/alkyne = 1:1.3:1.6; reactions were performed on 2 mmol of aldehyde in H_2O (3 mL) under microwave irradiation applying 100 W maximum power; [b] isolated yield.

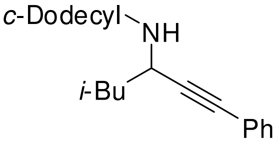
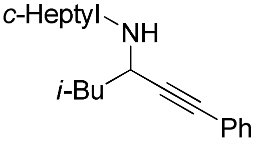
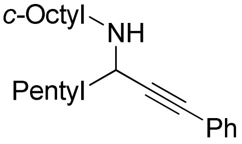
Next we evaluated the scope of this microwave-assisted Cu(I)/Cu(II)-catalyzed A^3-coupling protocol (Table 2). A variety of different amines, aldehydes and acetylenes was explored as partners in this coupling reaction applying the optimized conditions. In most cases the products were obtained in moderate to good yields. Remarkably, sterically hindered amines afforded the target secondary propargylamines in good yields (Table 2, entries 2, 5).

Table 2. Scope of the Protocol



Entry	Compound	Product	Yield, %[c]
1	4a[a]		85
2	4b[a]		64
3	4c[a]		41
4	4d[a]		72
5	4e[a]		59
6	4f[a]		83
7	4g[a]		85
8	4h[a]		84

9	**4i^{a}**		**87**
10	**4j^{a}**		**89**
11	**4k^{a}**		**73**
12	**4l^{a}**		**66**
13	**4m^{b}**		**78**
14	**4n^{b}**		**87**
15	**4o^{b}**		**81**
16	**4p^{b}**		**83**
17	**4q^{b}**		**74**
18	**4r^{b}**		**67**

19	**4s**[b]		**69**
20	**4t**[b]		**84**
21	**4u**[b]		**82**

[a]Molar ratio: aldehyde/amine/alkyne = 1:1.3:1.6; [b]molar ratio: aldehyde/amine/alkyne = 1:1.5:1.6; reactions were performed on 2 mmol of aldehyde in H_2O (3 mL) under microwave irradiation applying a ceiling temperature of 110°C and 100 W maximum power for 25 min, 10 mol% CuCl and 10 mol% $CuCl_2$; the resulting reaction mixture was extracted with EtOAc (20mL), dried and the residue was purified by column chromatography over silica gel; [c]isolated yield. PMB = 4-methoxybenzyl; PMP = 4-methoxyphenyl.

To expand the scope of amine substrates, we used different aldehydes and acetylenes as model substrates and examined various cyclic amines (Table 2, entries 13-21). However, due to lower activity of cyclic amines we increased their amount to 1.5 equiv The coupling proceeded smoothly, to afford the corresponding secondary propargylamines **4** in good yields.

The catalytic cycle proposed for this reaction involves condensation of amine and aldehyde with subsequent attack of the resulting imine by the metal acetylide formed from the terminal alkyne and CuCl. We assume that $CuCl_2$ plays a role as Lewis acid promoting both the imine formation and its activation for subsequent attack.[15b-d]

Conclusions

In summary, we have demonstrated a novel protocol for the preparation of secondary propargylamines using the relatively cheap Cu(I)/Cu(II) catalytic system and water as solvent. This microwave-assisted procedure offers several notable advantages including operational simplicity, high yields and little environmental impact.

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