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Efficient Microwave-Assisted Synthesis of Secondary Alkylpropargylamines by Using A^3-Coupling with Primary Aliphatic Amines

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Multicomponent reactions (MCRs) have attracted much attention in the framework of combinatorial chemistry owing to their synthetic efficiency, intrinsic atom economy, high selectivity and procedural simplicity. These reactions constitute a valuable approach for the creation of large libraries of structurally related, drug-like compounds, thereby enabling rapid lead identification and optimisation in drug discovery. They represent environmentally friendly processes by reducing the number of steps, energy consumption and waste production.[1]

The three-component coupling of an aldehyde, an alkyne and an amine, commonly called an A^3-coupling, is an MCR that has received much attention in recent years.[2] The resulting propargylamines are synthetically versatile key intermediates[3a,b] for the preparation of biologically active compounds and drugs.[3c–e] Classical methods for the synthesis of propargylamines use strong bases, such as butyllithium, organomagnesium reagents or lithium diisopropylamide (LDA), exploiting the relatively high acidity of the terminal acetylene to form alkynyl metal compounds. The stoichiometric quantities of the reagents required, as well as their high sensitivity to moisture, render these processes fairly unattractive.[4]

During recent years, substantial progress has been made in A^3-coupling reactions. Several transition-metal catalysts have been exploited that activate the C–H bond of the terminal alkyne. Ag^I salts,[5] Au^I/Au^{III} salts,[6] Au^{III}–salen (salen = N,N′-bis(salicylidene)ethylenediamine) complexes,[7] Cu^I salts,[8] Ir^I complexes,[9] Hg_2Cl_2,[10] Cu/Ru^{II} bimetallic systems,[11] $InCl_3$,[12] $ZnCl_2$,[13] $FeCl_3$[14] and nano CuO compounds[15] have all been used to run this reaction under homogeneous conditions. Moreover, Au^I, Ag^I and Cu^I in ionic liquids and supported Au^{III}, Ag^I, Cu^I and CuCl were successfully used to catalyse A^3-coupling reactions under heterogeneous conditions with preservation of the transition-metal catalyst.[16] Additionally, the enantioselective addition of terminal alkynes to imines provides access to optically active propargylamines. A variety of chiral ligands have been used for this reaction. High asymmetric induction has been reported by applying 1-(2-diphenylphosphino-1-naphthyl)isoquinoline (QUINAP) ligands.[17] In addition to these ligands, metal complexes of chiral amino acids,[18] chiral alcohols,[19] chiral binaphthylamines[20] and 2,6-bis(2-oxazolinyl)pyridine (PyBOX) ligand[21] have been used successfully.

Despite huge advancements, A^3-coupling reactions have mainly been optimised for reactions involving anilines and secondary amines, which result in the formation of *N*-arylpropargylamines or tertiary propargylamines. Primary amines are considered to be difficult substrates for A^3-coupling reactions; this limits access to secondary propargylamines.[22] Nevertheless, secondary alkylpropargylamines are potent synthetic intermediates that have mainly been explored for the synthesis of pyrrolidin,[23a] 5-alkylideneselenazolin-2-ones,[23b] pyrroles,[23c] quinolines[23d] and oxazolidinones.[23e] The synthesis of secondary alkylpropargylamines by using A^3-coupling reactions is scarcely reported in the literature[8c,23c,24–26] and, to the best of our knowledge, no systematic study has ever been described. Herein, we present an optimised protocol for the synthesis of secondary alkylpropargylamines by using a microwave-assisted A^3-coupling reaction.

In an optimisation study, benzylamine (**1{1}**) was used as a primary amine in combination with phenylacetylene (**2{1}**) and isobutyraldehyde (**3{1}**) (Table 1). As stated in the literature, the initial reagent ratio was selected as 1.3 equivalents of amine, 1.0 equivalent of aldehyde and 1.6 equivalents of alkyne[8c] with toluene as the solvent.[12,14] Reactions were carried out in the presence of different copper salts under microwave irradiation at various ceiling temperatures (Table 1). Relatively low concentrations of the CuI catalyst

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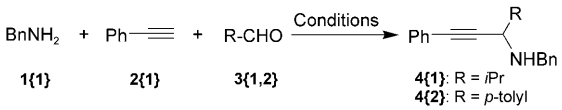
Table 1. Optimisation of the A^3-coupling reaction with benzylamine.[a]



Entry	Catalyst ([mol%])	T [°C]	R	Yield [%][b]
1	CuI (5)	80	*i*Pr	5
2	CuI (5)	100	*i*Pr	18
3	CuI (10)	80	*i*Pr	38
4	CuI (10)	100	*i*Pr	65
5	CuI (10)	120	*i*Pr	57
6	CuI (20)	100	*i*Pr	78
7	CuI (20)	120	*i*Pr	62
8	CuI (20)	100	*i*Pr	68[c]
9	CuI (20) + 4 Å molecular sieves	100	*i*Pr	57
10	CuI (20)	100	*i*Pr	57[d]
11	CuI (20)	100	*p*-tolyl	60
12	CuI (20)	100	*p*-tolyl	41[e]
13	CuI (20)	100	*p*-tolyl	55[f]
14	CuCl (20)	100	*i*Pr	73
15	CuCl (20)	100	*p*-tolyl	64
16	CuBr (20)	100	*i*Pr	68
17	CuBr (20)	100	*p*-tolyl	85
18	CuOAc (20)	100	*i*Pr	34
19	CuOTf (20)	100	*i*Pr	21
20	$Cu(OTf)_2$ (20)	100	*i*Pr	30
21	$InCl_3$ (20)	100	*i*Pr	–
22	$FeCl_3$ (20)	100	*i*Pr	–

[a] Reaction conditions using isobutyraldehyde: amine (1.3 mmol), isobutyraldehyde (1.0 mmol), alkyne (1.6 mmol), CuBr (0.05, 0.1 and 0.20 mmol), toluene (1.0 mL), MW, 80 W, 25 min; reaction conditions using 4-methylbenzaldehyde: amine (1.5 mmol), 4-methylbenzaldehyde (1.0 mmol), alkyne (3.0 mmol), CuBr (0.20 mmol), toluene (1.0 mL), MW, 80 W, 25 min. [b] Isolated yields after column chromatography. [c] Irradiation was continued for 50 min. [d] The reaction mixture was conventionally heated for 17 h. [e] Irradiation was continued for 40 min. [f] The reaction mixture was irradiated without solvent.

resulted in low yields of the propargylamine **4{1}** (Table 1, entries 1–5). The optimal concentration of this catalyst was found to be 20 mol% (Table 1, entry 6) yielding the desired propargylamine, **4{1}**, in 78% yield. Other attempts to improve the yield by increasing the reaction temperature (Table 1, entry 7), increasing the irradiation time (Table 1, entry 8) or by using molecular sieves (Table 1, entry 9) did not improve the yield. When the reaction was conducted under conventional heating for 17 h, the desired propargylamine, **4{1}**, was obtained in moderate yield together with multiple unidentified byproducts (Table 1, entry 10). Other readily available Cu^I salts, such as CuCl and CuBr, also gave competitive yields (Table 1, entries 14 and 16, respectively), whereas CuOAc, CuOTf and $Cu(OTf)_2$ gave the desired product in poor yields (Table 1, entries 18, 19 and 20, respectively). The application of $InCl_3$ did not yield any trace of the product (Table 1, entry 21).[12] Finally, we tried the recently reported catalyst $FeCl_3$, which is described as being very efficient in reactions involving secondary amines.[14] Unfortunately, this catalyst did not work for our reaction with benzylamine (Table 1, entry 22). The use of more polar solvents, such as THF or EtOH, resulted in low yields due to the formation of multiple unidentified byproducts.

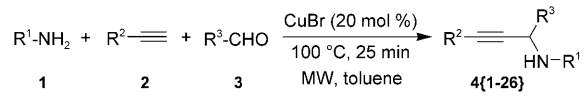
Surprisingly, applying these optimised conditions (as in Table 1, entry 6) to perform the A^3-coupling reaction with 4-methylbenzaldehyde, **3{2}**, resulted in a low yield of the corresponding propargylamine, **4{2}** (Table 1, entry 11). The lower yield can be attributed to the high reactivity of the resulting secondary propargylamine, which, as indicated by the mass spectrum of the reaction mixture, further reacts with aldehyde and acetylene to give a dimeric propargylamine.[22] Therefore, modified reagent ratios and alternative Cu^I catalysts were evaluated. The reaction was first run with 1.5 equivalents of amine, 1.0 equivalent of aldehyde and 3 equivalents of alkyne. By using 20 mol% CuCl, the product, **4{2}**, was obtained in a slightly improved yield of 64% (Table 1, entry 15). Neither an increase of the irradiation time nor irradiation of the neat reaction mixture improved the yield (Table 1, entries 12 and 13). However, when 20 mol% of CuBr was used, the desired propargylamine, **4{2}**, was obtained in an excellent 85% yield (Table 1, entry 17). As CuBr is air sensitive under the microwave irradiation conditions generally used for the reaction,[27] it is necessary to perform these reactions in an inert atmosphere.

Next we evaluated the scope of this microwave-assisted CuBr-catalysed A^3-coupling protocol (Table 2). A variety of primary alkyl- and cycloalkylamines were evaluated (Table 2, entries 3–12). Good yields were obtained, except in the case of dodecylamine (Table 2, entry 10). Heterocyclic and aliphatic acetylenes were also explored as partners in the A^3-coupling reaction, but only yielded the target compounds, **4**, in moderate yields due to the formation of unidentified side products (Table 2, entries 15–17). To expand the scope of the protocol, a variety of aliphatic aldehydes were also evaluated. The reactions proceeded smoothly, delivering the corresponding propargylamines in 64–86% yields (Table 2, entries 18–26).

A tentative mechanism for the CuBr-catalysed, one-pot, three-component A^3-coupling is proposed in Scheme 1. The CuBr catalyst reacts with the alkyne to form an alkynylcopper(I) complex and release HBr. Microwave irradiation is necessary to speed up the A^3-coupling as well as for the formation of the alkynylcopper and the imine.[8c] The A^3-coupling using a primary amine is thought to commence with the in situ formation of an imine and subsequent attack by alkynylcopper via transition state **A** (Scheme 1). After intramolecular transfer of the alkyne moiety to the imine, the copper-complexed product **B** is formed. Decomplexation produces the free propargylamine **C** and regenerates the Cu^I catalyst.[24] Secondary propargylamine **C** is a highly reactive A^3-coupling partner and, in the presence of excess aldehyde, can easily produce iminium salt **D**. Subsequent attack on **D** by alkynylcopper would give the tertiary propargylamine **E** (Scheme 1). Because of this unwanted side reaction, all the A^3-coupling reactions were performed by using excess amine and acetylene.

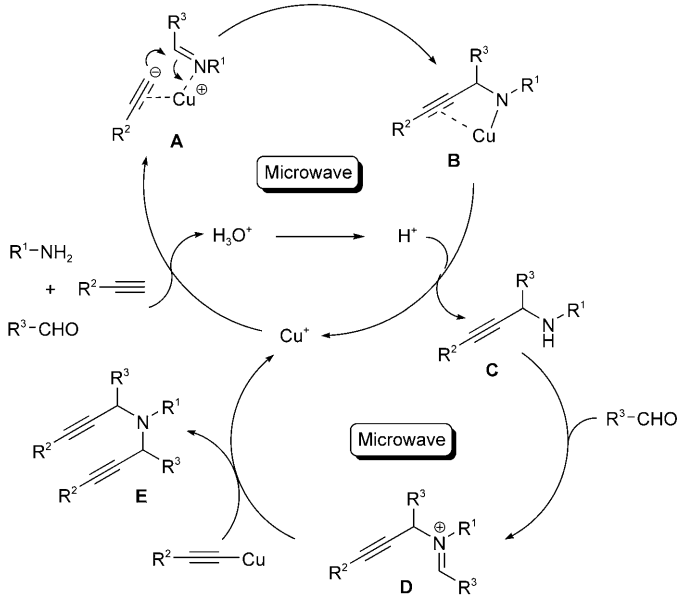
To conclude, we have successfully developed an efficient, fast and economical one-pot A^3-coupling protocol applying primary aliphatic amines that provides access to secondary alkylpropargylamines in high yields. The reactions were car-

Table 2. Scope and limitations of the microwave-assisted CuBr-catalysed A^3-coupling reactions.[a]



Entry	R^1	R^2	R^3	Yield [%][b]
1	Bn	Ph	*i*Pr	89
2	Bn	Ph	*p*-tolyl	85
3	Pr	Ph	*i*Bu	94
4	3-methoxyphenethyl	Ph	*i*Bu	66
5	*t*Bu	Ph	*i*Bu	73
6	cycloheptyl	Ph	*i*Bu	72
7	cyclododecyl	Ph	*i*Bu	68
8	*p*-methoxybenzyl	Ph	*i*Bu	60
9	*i*Bu	Ph	*i*Bu	67
10	dodecyl	Ph	*i*Bu	46
11	cyclooctyl	Ph	pentyl	83
12	Bn	*p*-tolyl	*i*Pr	69
13	*p*-methoxybenzyl	*p*-(*t*Bu)Ph	*p*-FPh	89
14	Bn	*p*-pentyloxyphenyl	*p*-tolyl	62
15	Bn	thiophene-3-yl	Ph	42
16	Bn	Bn	Ph	44
17	Bn	cyclopentyl	Ph	41
18	Bn	Ph	Et	86
19	Bn	Ph	Pr	73
20	Bn	Ph	Bu	65
21	Bn	Ph	*i*Bu	78
22	Bn	Ph	pentyl	77
23	Bn	Ph	octyl	83
24	Bn	Ph	decyl	75
25	Bn	Ph	cyclopropyl	64
26	Bn	Ph	cyclohexyl	85

[a] Reaction conditions: alkyne **1** (3.0 mmol), aldehyde **2** (1.0 mmol), amine **3** (1.5 mmol), CuBr (0.20 mmol, 57 mg), toluene (1.0 mL), MW, 80 W, 100 °C, 25 min; [b] Isolated yields after column chromatography.



Scheme 1. Proposed A^3-coupling reaction mechanism under microwave irradiation conditions.

ried out in the presence of catalytic amounts of CuBr without the use of any ligand under microwave irradiation. The reactions were also applicable to sterically hindered amines and aldehydes.

Experimental Section

General procedure for the preparation of alkyl-substituted propargylamines: Amine (1.5 mmol), aldehyde (1.0 mmol), acetylene (3.0 mmol), copper bromide (0.2 mmol) and toluene (1.0 mL) were added to a microwave vial equipped with a magnetic stirring bar. The mixture was degassed and backfilled with argon. The reaction vessel was sealed and irradiated in the cavity of a CEM-Discover microwave reactor for 25 min at a ceiling temperature of 100 °C and a maximum power of 80 W. The resulting reaction mixture was cooled to ambient temperature, diluted with dichloromethane (2 mL), loaded on a silica gel column and flash filtered with 10–20 % EtOAc in heptane to afford the product as a light yellow oil. The identity and purity of the products was confirmed by ^{1}H and ^{13}C NMR spectroscopies and high-resolution mass spectrometry (see the Supporting Information for full details).

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Keywords: A^3-coupling · microwave chemistry · multicomponent reactions · propargylamines · synthetic methods

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