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Copper(I)-Catalyzed Decarboxylative Coupling of Propiolic Acids with Secondary Amines and Aldehydes

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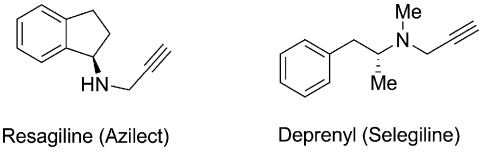
An efficient microwave-assisted synthesis of tertiary propargylamines has been developed by copper(I)-catalyzed decarboxylative A^3-coupling reaction of an alkynylcarboxylic acid with a secondary amine and an aldehyde. A wide range of diversely substituted propargylamines could be synthesized in high yields. The optimal reaction conditions are also effective for 3-alkylpropiolic acids and for terminal propiolic acid.

Introduction

Multicomponent reactions (MCRs) have attracted much attention in the framework of combinatorial 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, which enable rapid lead identification and lead optimization in drug discovery. MCRs provide a viable synthetic strategy to access complex structures from rather simple starting materials through one-pot methodology, and in particular exhibit high atom economy and selectivity.[2] A typical example of such a process is the three-component coupling of an aldehyde, an amine and an alkyne (A^3-coupling) through C–H activation to afford propargylamines.[3–7]

Several propargylamines have been shown to be highly potent and irreversible selective monoamine oxidase type-B inhibitors[8] (Figure 1). These compounds have been used for the treatment of neuropsychiatric disorders such as Alzheimer's and Parkinson's disease.

Propargylamines are generally used in organic synthesis as precursors and versatile building blocks for the preparation of nitrogen-containing heterocyclic compounds such as pyrrolidines,[9] pyrroles,[10] oxazolidinones,[11] aminoindolizines[12] and 2-aminoimidazoles.[13] They also act as key intermediates[14] for the construction of biologically active compounds like isosteres, β-lactams, oxotremorine substrates, conformationally restricted peptides, and therapeutic drug molecules.[15] Traditionally, propargylamines are synthesized by nucleophilic attack of lithium acetylides or Grignard reagents to imines.[16]



Resagiline (Azilect) Deprenyl (Selegiline)

Figure 1. Propargylamine inhibitors of type-B monoamine oxidase.

In recent years, enormous progress has been made to expand the scope of the direct addition of alkynes to carbon–nitrogen double bonds either from prepared imines or from aldehydes and amines in a one-pot procedure with various transition-metal catalysts through C–H activation of terminal alkynes. These include Ag^I salts,[17] Au^I/Au^{II} salts,[18] Au^{III}–salen complexes,[19] Cu^I salts,[20] Hg_2Cl_2,[21] and Cu/Ru dimetallic systems[22] under homogeneous conditions. Recently, Au^{III}[23] and Ag^I[24] in ionic liquids were used to catalyze A^3-coupling reactions. Also, more sophisticated alternative energy sources like microwave[7] and ultrasonic[25] irradiation have been used in the presence of Cu^I salt.

Despite its great potential, Cu^I-catalyzed decarboxylative strategies are rarely used for the formation of C–C bonds through A^3-coupling reaction.[26] Recently, the group of Sunwoo Lee reported a metal-free decarboxylative A^3-coupling reaction between a propiolic acid, a secondary amine and paraformaldehyde.[27] There is a limited number of literature examples in which alkynes with a short alkyl chain are employed in the A^3-coupling reaction. To the best of our knowledge, only one example of a terminal propargyl-

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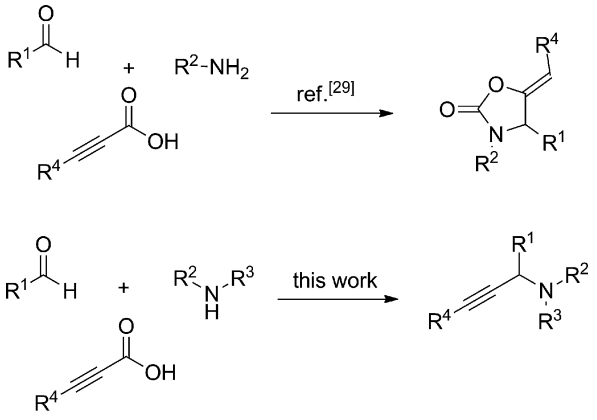
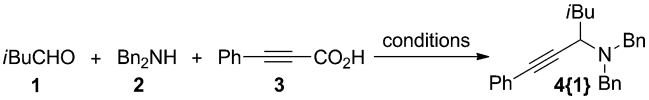
amine was reported that uses trimethylsilylacetylene.[28] In this regard, our group recently discovered that a Cu^I-catalyzed decarboxylative coupling reaction could be used efficiently to obtain oxazolidin-2-ones from a propiolic acid, a primary amine and an aldehyde in a one-pot fashion (Scheme 1).[29] Herein we report a broadly applicable microwave-assisted Cu^I-catalyzed decarboxylative coupling reaction of a propiolic acid with a secondary amine and an aldehyde to synthesize diversely substituted tertiary propargylamines (Scheme 1).



Scheme 1.

Table 1. Optimization of the reaction conditions for decarboxylative A^3-coupling.[a]



Entry	Catalyst [mol-%]	Time [min]	Temperature [°C]	Yield [%][b]
1	20% CuBr	15	100	74
2	20% CuCl	15	100	72
3	20% CuOAc	15	100	34
4	20% CuI	15	100	82
5	20% $Cu(MeCN)_4PF_6$	15	100	77
6	20% CuOTf	15	100	52
7	20% $Cu(OTf)_2$	15	100	73
8	20% CuTC[c]	15	100	35
9	10% CuI	15	100	63
10	5% CuI	15	100	50
11	20% CuI	15	80	80
12	20% CuI	15	120	73
13	20% CuI	40	100	76
14	20% CuI	6 h	100	79[d]
15	no catalyst	15	100	0

[a] Reactions were performed on a 1 mmol scale with isovaleraldehyde, dibenzylamine and phenylpropiolic acid (1:1.2:1.5) in toluene (1 mL) under microwave irradiation at 100 W maximum power. [b] Isolated yields based on isovaleraldehyde. [c] CuTC = copper(I) thiophene-2-carboxylate. [d] Conventional heating.

Results and Discussion

Initially, we studied the coupling of isovaleraldehyde (**1**), dibenzylamine (**2**) and 3-phenylpropiolic acid (**3**) in toluene at 100 °C in the presence of CuBr (20 mol-%) under microwave irradiation (Table 1). To our delight, the desired product **4{1}** was obtained in 74% yield within 15 min (Table 1, Entry 1). To improve the yield, various copper(I) and copper(II) salts were examined (Table 1, Entries 2–8), which were shown to be effective for similar reactions.[30] Among them, CuI provided the highest yield (Table 1, Entry 4). When the reactions were performed with lower catalyst loadings, decreased yields were obtained (Table 1, Entries 9 and 10). Different temperatures were also tested, but did not improve the yields (Table 1, Entries 11 and 12). Remarkably, $Cu(OTf)_2$ was slightly less efficient than CuI (Table 1, Entry 7).[31] Finally, when the reaction was conducted by using conventional heating under the same conditions, the desired propargylamine **4{1}** was obtained in a yield of 79% after an extended reaction time of 6 h (Table 1, Entry 14). Remarkably, no product was observed in the absence of catalyst (Table 1, Entry 15).

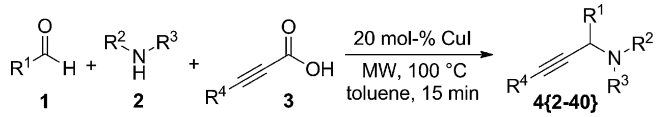
To investigate the scope of this decarboxylative A^3-coupling reaction, various aldehydes **1** were examined under the above optimized conditions (Table 1, Entry 4).[31] For aliphatic aldehydes, the reaction afforded the corresponding products **4** in moderate to good yields (Table 2, Entries 1–6). The use of aromatic 1-naphthaldehyde gave the product in decreased yield (Table 2, Entry 7). The reactions of isovaleraldehyde and 3-phenylpropiolic acid were examined with different secondary amines. The corresponding coupling products were obtained in high yields (Table 2, Entries 8–17). Only trace amounts of by-products, which resulted from the Michael addition of amine to propiolic acid, were observed by ^1H NMR spectroscopy and GC–MS of the crude reaction mixtures.

Subsequently, our investigations were focused on the use of various 3-substituted propiolic acids **3**. When 3-alkylpropiolic acids were used, the corresponding products **4** were obtained in good yields (Table 2, Entries 18–25).

Surprisingly, the use of 3-methylpropiolic acid in this decarboxylative procedure represents an elegant alternative for the application of gaseous and explosive propyne in a classical A^3-coupling reaction (Table 2, Entry 18; R^4 = Me). Similarly, 3-triisopropylsilylpropiolic acid was also applicable (Table 2, Entry 25). The best yields were obtained when 3-aryl-substituted propiolic acids were used (Table 2, Entries 26–28). Encouraged by these results, we then tried to combine various aldehydes **1** and amines **2** with propiolic acids **3** in this coupling process. We were pleased to find that most of the combinations led to the formation of the desired products in good to excellent yields (Table 2, Entries 29–34). Finally, the use of the terminal propiolic acid (Table 2, Entries 35–39; R^4 = H) afforded the corresponding coupling products in 43–78% yields.

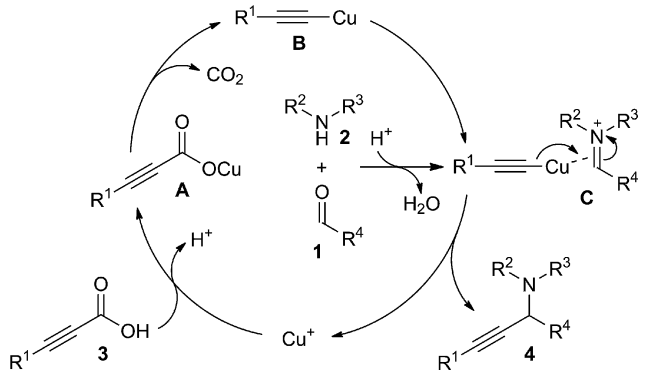
A tentative mechanism for the Cu^I-catalyzed one-pot three-component decarboxylative coupling reaction is proposed in Scheme 2.[32] The Cu^I catalyst reacts with the alk-

Table 2. Scope of the decarboxylative A^3-coupling reaction.[a]



Entry	Aldehyde **1**	Amine **2**	R$^{4[b]}$	Yield [%][c]
1	isobutyraldehyde	dibenzylamine	Ph	45
2	butyraldehyde	dibenzylamine	Ph	65
3	valeraldehyde	dibenzylamine	Ph	63
4	hexanal	dibenzylamine	Ph	64
5	cyclohexanecarbaldehyde	dibenzylamine	Ph	61
6	3-phenylpropionaldehyde	dibenzylamine	Ph	57
7	1-naphthaldehyde	dibenzylamine	Ph	25
8	isovaleraldehyde	morpholine	Ph	89
9	isovaleraldehyde	piperidine	Ph	88
10	isovaleraldehyde	4-methylpiperidine	Ph	94
11	isovaleraldehyde	1,4-dioxa-8-azapirodecane	Ph	82
12	isovaleraldehyde	1-benzylpiperazine	Ph	86
13	isovaleraldehyde	diethylamine	Ph	90
14	isovaleraldehyde	dibutylamine	Ph	91
15	isovaleraldehyde	dihexylamine	Ph	80
16	isovaleraldehyde	*N*-methylbenylamine	Ph	93
17	isovaleraldehyde	*N*-allylmethylamine	Ph	92
18	isovaleraldehyde	dibenzylamine	Me	78
19	isovaleraldehyde	dibenzylamine	Et	85
20	isovaleraldehyde	dibenzylamine	Pr	88
21	isovaleraldehyde	dibenzylamine	*i*Pr	78
22	isovaleraldehyde	dibenzylamine	*t*Bu	76
23	isovaleraldehyde	dibenzylamine	amyl	72
24	isovaleraldehyde	dibenzylamine	hexyl	79
25	isovaleraldehyde	dibenzylamine	TIPS	74
26	isovaleraldehyde	dibenzylamine	2-naphthyl	95
27	isovaleraldehyde	dibenzylamine	PMP	90
28	isovaleraldehyde	dibenzylamine	4-tolyl	92
29	cyclohexanecarbaldehyde	4-methylpiperidine	Ph	96
30	cyclohexanecarbaldehyde	*N*-allylmethylamine	Ph	91
31	3-phenylpropionaldehyde	morpholine	Ph	70
32	3-phenylpropionaldehyde	4-methylpiperidine	Ph	86
33	valeraldehyde	4-methylpiperidine	Ph	84
34	isobutyraldehyde	piperidine	Ph	91
35	valeraldehyde	tetrahydroisoquinoline	H	72
36	isovaleraldehyde	tetrahydroisoquinoline	H	68
37	isobutyraldehyde	dibenzylamine	H	74
38	benzaldehyde	*N*-methylbenzylamine	H	64
39	isovaleraldehyde	*N*-methylbenzylamine	H	78

[a] A mixture of aldehyde (1 mmol), amine (1.2 mmol), alkyne (1.5 mmol), CuI (20 mol-%) in toluene (1 mL) was irradiated at a maximum temperature of 100 °C and a maximum power of 100 W for 15 min. [b] TIPS = triisopropylsilyl; PMP = *p*-methoxyphenyl. [c] Isolated yields based on aldehydes are reported.

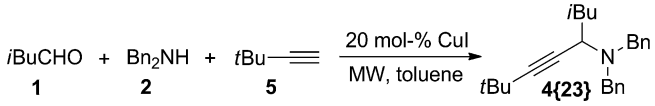


Scheme 2. Tentative mechanism for the decarboxylative A^3-coupling reaction.

ynylcarboxylic acid **1** to form the copper carboxylate **A**, which undergoes decarboxylation at elevated temperature to provide the reactive alkynylcopper species **B**. The copper acetylide **B** attacks the in situ formed iminium salt **C** to result in the formation of the propargylamine **4** and regeneration of the Cu^{I} catalyst.

To prove the mechanism we carried out a comparative study by using 3,3-dimethylbut-1-yne (**5**) as an alkyne equivalent of 4,4-dimethylpent-2-ynoic acid under microwave irradiation (Table 3). By applying similar reaction conditions as for the decarboxylative A^3-coupling reaction, the desired product **4{23}** was obtained in only 52% isolated yield (Table 3, Entry 2). Comparable yields were achieved only after 35 min at 100 °C (Table 3, Entry 4) or after 15 min at 120 °C (Table 3, Entry 7).

Table 3. Comparative study of a classical A^3-coupling reaction.[a]



Entry	Time [min]	Temperature [°C]	Yield [%][b]
1	10	100	43
2	15	100	52
3	25	100	64
4	35	100	77
5	45	100	82
6	15	110	74
7	15	120	78

[a] Reactions were performed on a 1 mmol scale with isovaleraldehyde, dibenzylamine and 3,3-dimethylbut-1-yne (1:1.2:1.5) in toluene (1 mL) under microwave irradiation at 100 W maximum power. [b] Isolated yields based on isovaleraldehyde.

Conclusions

We have developed a microwave-assisted three-component reaction protocol for the selective preparation of diversely substituted tertiary propargylamines by starting from an alkynylcarboxylic acid, an alkyne and an amine. This efficient protocol involves the decarboxylative formation of an alkynylcopper intermediate as an alternative to the classic C_{sp}–H bond activation followed by an A^3-coupling reaction. Importantly, this approach extends the scope of the A^3-coupling reaction to terminal and short alkyl-substituted propargylamines.

Experimental Section

Aldehyde **1** (1 mmol), amine **2** (1.2 mmol), and propiolic acid **3** (1.5 mmol) were dissolved in toluene (1.0 mL) in a microwave vial containing a magnetic stir bar, and then copper iodide (38 mg, 0.2 mmol) was added. The reaction vessel was sealed and irradiated in the cavity of a CEM Discover microwave reactor at a maximum temperature of 100 °C and a maximum power of 100 W for 15 min. The resulting reaction mixture was loaded onto a silica gel column and eluted with 6–10% EtOAc in heptanes to afford the desired product **4** as light yellowish oil.

Supporting Information (see footnote on the first page of this article): General information, synthesis of propargylamines **4**, spectroscopic data of propargylamines **4**, ^{1}H NMR and ^{13}C NMR spectra of propargylamines **4**.

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