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Metal-Free Decarboxylative Three-Component Coupling Reaction for the Synthesis of Propargylamines

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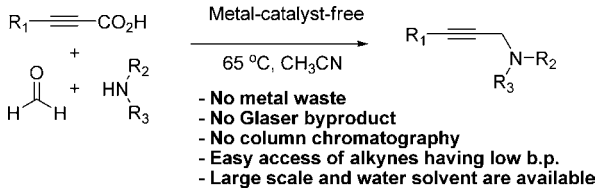
ABSTRACT



A metal-free decarboxylative three-component coupling reaction was developed. When alkynyl carboxylic acids, paraformaldehyde, and amines were reacted in CH_3CN at 65 °C for 3 h, the desired propargylamines were obtained in good yields. This coupling reaction also showed good yield in water solvent. This reaction showed higher selectivity toward alkynyl carboxylic acids than a terminal alkyne.

A number of decarboxylative coupling reactions have been developed for the formation of C−C, C−N, C−S, and C−P bonds.[1] A variety of carboxylic acids such as alkyl, aryl, benzyl, and alkynyl carboxylic acids have been employed as coupling substrates and have exhibited good activity in coupling reactions. Much attention has been paid to decarboxylative coupling due to the release of CO_2, which is less harmful than the metal waste derived from the classical organometallic coupling substrates. However, most of the decarboxylative coupling reactions that have been reported so far have still required transition-metal catalysts, which give rise to the release of metal waste in the process (Scheme 1, reaction 1). Therefore, the development of a metal-free system has been needed.

Recently, we developed the palladium-catalyzed decarboxylative coupling reaction of alkynyl carboxylic acids and the efficient methods for the synthesis of diaryl alkynes,[2] diynes,[3] alkynyl ketones,[4] and aryl propiolic acids.[5] In the course of our effort to expand the decarboxylative coupling reactions, we found that phenyl propiolic acid was decarboxylated to produce phenyl acetylene in the absence of metal when the reaction was run with an organic base at 80 °C.[6]

From this result, we envisioned that alkynyl carboxylic acid could be transformed to the activated terminal alkyne in the absence of metal. With this concept in mind, we have focused on developing a metal-free decarboxylative coupling for the synthesis of propargylamine.

Propargylamines are important building blocks for the synthesis of heterocyclic compounds bearing nitrogen atoms, such as pyrroles,[7] pyrrolidine,[8] pyrrolophane,[9]

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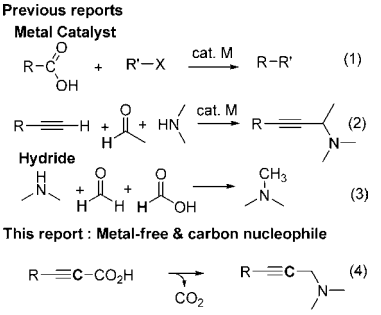
aminoindolizine,[10] 2-aminoimidaozels,[11] and oxazolidinones[12] and work as key elements for the construction of natural products and biologically active compounds, such as therapeutic drug molecules.[13] There are several classical methods for the preparation of propargylamines.[14] However, these methods have some drawbacks, such as the requirement of a stoichiometric amount of metal reagents, moisture sensitivity, and low functional-group tolerance. To solve these problems, the transition-metal-catalyzed three-component coupling of an aldehyde, amine, and alkyne (A^3 coupling) has been developed and widely used under mild conditions. (Scheme 1, reaction 2). Therefore, there has been much effort to develop efficient transition metal catalysts for the C−H bond activation of terminal alkyne. Several transition metals such as copper,[15] gold,[16] silver,[17] iridium,[18] indium,[19] iron,[20] and zinc[21] have been used in such three-component reactions. However, there are intrinsic drawbacks with the employment of metal, which give rise to problems regarding environmental pollution, cost, and complication in the purification processes. Moreover, the employment of metal catalysts occasionally affords the Glaser homocoupling compound as a byproduct, which gives rise to a decrease in the yield of the product. Although base-catalyzed synthesis of propargylamine from terminal acetylene has been reported, DMSO was employed as the solvent which is not a good solvent for the purification step.[22] In addition, it is not easy to use highly volatile terminal alkynes such as 1-propyne and 1-butyne, even in the case of metal-catalyzed A^3 coupling. To overcome these problems, we report a metal-free decarboxylative three-component coupling reaction for the synthesis of propargylamine from the three-component reaction of an amine, aldehyde, and alkynyl carboxylic acid. To the best of our knowledge, this reaction is the first example of the employment of a carbon nucleophile in Eschweiler−Clarke methylation (Scheme 1, reaction 3).[23]

Scheme 1. Metal-Free Decarboxylative Coupling



To this end, phenyl propiolic acid, paraformaldehyde, and morpholine were chosen as model substrates. A variety of solvents were first screened, as shown in Table 1. When an equal amount of phenyl propiolic acid, paraformaldehyde, and morpholine were reacted in DMSO, which was a good solvent in the decarboxylative coupling reaction, the desired product was formed in 15% yield at 65 °C (entry 1). A variety of solvents were tested (entries 2−7). Among them, CH_3CN showed the best result and afforded phenyl propargyl amine **3aa** in 83% yield. An attempt to add a base to accelerate the decarboxylation of phenyl propiolic acid resulted in no product (entries 8−10). However, when the reaction was run under acidic conditions with acetic acid and benzoic acid, the yields were similar, regardless of the amount of acid used (entries 11−13). When the ratios of the three starting materials were varied, 1.2 equiv of phenyl propiolic acids and paraformaldehyde and 1.0 equiv of morpholine produced an almost quantitative yield of product (entry 16). With decreasing reaction temperature, the yields of product decreased (entries 17 and 18). Interestingly, the desired product was formed with 97% yield even in water solvent at 100 °C (entry 19). When phenyl acetylene was employed instead of phenyl propiolic acid, a trace amount of desired product was formed (entry 20). To investigate the metal-free conditions in this reaction solution, the solution was subjected to ICP-MS. The concentration of transition metal ions in the solution was below the detection limit of the instrument, so the metal concentrations were estimated to not exceed hundreds of ppb.

With these optimized conditions, a variety of secondary amines were evaluated in the three-component coupling reaction. The results are summarized in Scheme 2. First,

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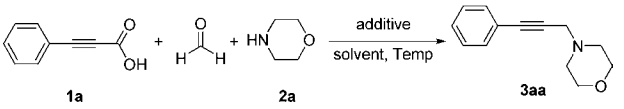
Table 1. Optimized Metal-Free Conditions for the Synthesis of Propargylamine **3aa**[a]



entry	ratio[b]	solvent	additive[c]	temp	yield (%)[d]
1	1.0/1.0/1.0	DMSO	–	65	15
2	1.0/1.0/1.0	toluene	–	65	44
3	1.0/1.0/1.0	THF	–	65	48
4	1.0/1.0/1.0	dioxane	–	65	54
5	1.0/1.0/1.0	$ClCH_2CH_2Cl$	–	65	73
6	1.0/1.0/1.0	EtOH	–	65	54
7	1.0/1.0/1.0	CH_3CN	–	65	83
8	1.0/1.0/1.0	CH_3CN	DBU	65	0
9	1.0/1.0/1.0	CH_3CN	Et_3N	65	0
10	1.0/1.0/1.0	CH_3CN	Cs_2CO_3	65	0
11	1.0/1.0/1.0	CH_3CN	AcOH	65	76
12[e]	1.0/1.0/1.0	CH_3CN	AcOH	65	77
13	1.0/1.0/1.0	CH_3CN	$PhCO_2H$	65	78
14	1.0/1.2/1.2	CH_3CN	–	65	78
15	1.2/1.0/1.2	CH_3CN	–	65	84
16	1.2/1.2/1.0	CH_3CN	–	65	98
17	1.2/1.2/1.0	CH_3CN	–	55	79
18	1.2/1.2/1.0	CH_3CN	–	25	11
19	1.2/1.2/1.0	H_2O	–	100	97
20[f]	1.2/1.2/1.0	CH_3CN	–	65	trace

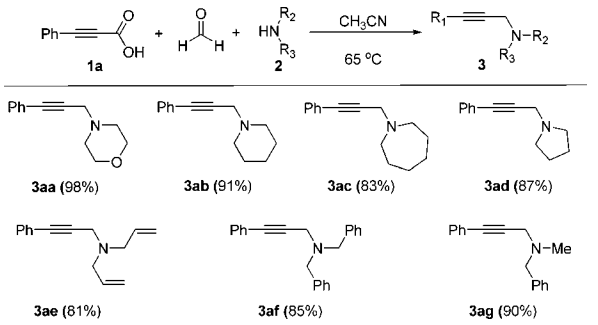
[a] Reaction conditions: The limiting reagent was employed at 3.0 mmol scale. [b] Ratio of **1a**/paraformaldehyde/**2a**. [c] 3.0 mmol of additives. [d] Isolated yield. [e] 3 mL of AcOH. [f] Phenylacetylene was used instead of **1a**.

secondary amines were reacted with phenyl propiolic acid and paraformaldehyde in CH_3CN at 65 °C. As expected, all secondary amines afforded the corresponding phenyl propargyl amines in good yields. Cyclic amines such as morpholine (**2a**), piperidine (**2b**), azepane (**2c**), and pyrrolidine (**2d**) afforded the corresponding phenylpropagyl amines in 98%, 91%, 83%, and 87% yields, respectively. Diallylamine (**2e**), dibenzylamine (**2f**), and *N*-methylbenzylamine (**2g**) showed good yields in the formation of **3ae**, **3af**, and **3ag**. In addition, to evaluate the feasibility of this reaction system on a large scale, we conducted the synthesis of **3aa** at the 20 g scale. The desired product **3aa** was obtained in 98% yield without column chromatography.

Next, substituted aryl alkynyl carboxylic acids[5] were employed in the three-component coupling reaction as shown in Scheme 3.

2-Butynoic acid (**1b**) and 2-pentynoic acid (**1c**), which were propyne and butyne surrogates, respectively, gave the desired coupled products in 84% and 81% yields, respectively. 2-Octynoic acid (**1d**) produced **3da** in 76% yield. *Para*- and *ortho*-tolyl propiolic acids coupled with paraformaldehyde and morpholine to produce the corresponding propargyl amines **3ea** and **3fa** in 98% and 91% yields, respectively. Methoxy-, bromo-, and chloro-substituted phenyl propiolic acids showed good product yields. Aryl propiolic acids with electron-withdrawing groups such as nitro, nitrile, ketone, ester, and aldehyde afforded the

Scheme 2. Synthesis of Propargylamines Form a Variety of Amines[a]

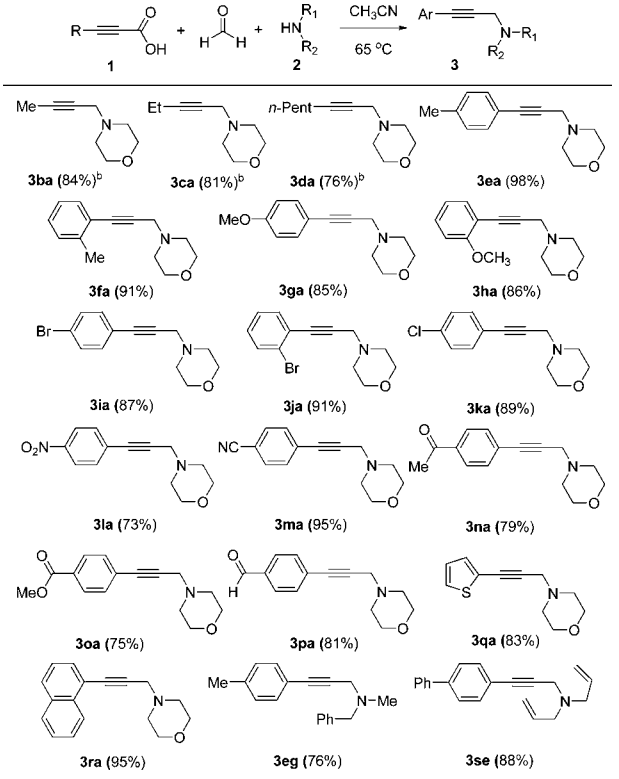


[a] Reaction conditions: **1** (6.0 mmol), paraformaldehyde (6.0 mmol), and **2** (5.0 mmol) were reacted in CH_3CN at 65 °C for 3 h.

desired coupled products **3la**, **3ma**, **3na**, **3oa**, and **3pa** in good yields. 2-Thiophenyl (**3q**) and 1-naphthyl propiolic acids (**3r**) gave the desired products in 83% and 95% yields, respectively. The substituted phenyl propiolic acids **3e** and **3s** coupled with *N*-methylbenzyl amine and diallylamine to produce the corresponding propargyl amines in good yields.

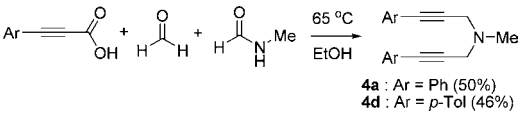
When *N*-methyl formamide was employed as an amine source, dipropargyl-substituted amines were formed in good

Scheme 3. Synthesis of Propargylamines from a Variety of Alkynyl Carboxylic Acids[a]

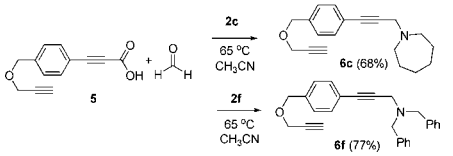


[a] Reaction conditions: **1** (6.0 mmol), paraformaldehyde (6.0 mmol) and **2** (5.0 mmol) were reacted in CH_3CN at 65 °C for 3 h. [b] **1** (7.5 mmol) was employed and the reaction temperature was 90 °C.

Scheme 4. Double Propargylation of *N*-Methylformamide



Scheme 5. Selective Coupling Reaction toward Alkynyl Carboxylic Acid

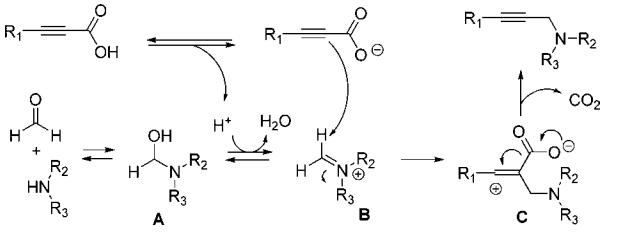


yields. As shown in Scheme 4, phenyl propiolic acid and *p*-tolyl propiolic acid gave the corresponding dipropargyl amines **4a** and **4d** in 50% and 46% yields. The transformation of both methylenes from the paraformaldehyde was defined using D_2CO experiments.

The result of entry 20 in Table 1, with no coupled product from the terminal alkyne in the metal-free conditions, is expected to afford the selective coupling reaction toward alkynyl carboxylic acids, even in the presence of a terminal alkyne. As expected, when propiolic acid **5** bearing a terminal alkyne was reacted with paraformaldehyde and azepane (**2c**) or dibenzylamine (**2f**), the desired products **6c** and **6f**, which have a terminal alkyne, were afforded in 68% and 77% yields, respectively (Scheme 5).

We propose a mechanism for the metal-free, one-pot, three-component decarboxylative coupling reaction as shown in Scheme 6. This is similar with the mechanism of Eschweiler–Clarke methylation.[23] The reaction with an aldehyde and amine generated the corresponding hemiaminal **A**. The acid proton of an alkynyl carboxylic acid accelerates the formation of iminium salt **B**. The alkynyl carbon bonded to carboxylate attacks iminium salt **B** to

Scheme 6. Proposed Mechanism



form intermediate **C** and then affords the desired propargylamine through decarboxylation.

In summary, we have developed metal-free conditions for the synthesis of propargylamine from the one-pot, three-component reaction of an aldehyde, amine, and alkynyl carboxylic acid. This reaction system has several advantages as follows: (1) no column chromatography method is needed to purify the final product. Therefore, a large scale reaction is feasible; (2) no metal waste was released; (3) the Glaser byproduct occasionally observed in metal-catalyst systems was not formed; (4) the employment of an alkynyl carboxylic acid as a surrogate for alkynes having a low boiling point was effective for easy handling; (5) the survival of the terminal alkyne and benzaldehyde offered the opportunity for further functionalization. To the best of our knowledge, this is the first report of a metal-free system in the decarboxylative coupling reaction.

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.