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Glyoxylic Acid: A Carboxyl Group-Assisted Metal-Free Decarboxylative Reaction Toward Propargylamines

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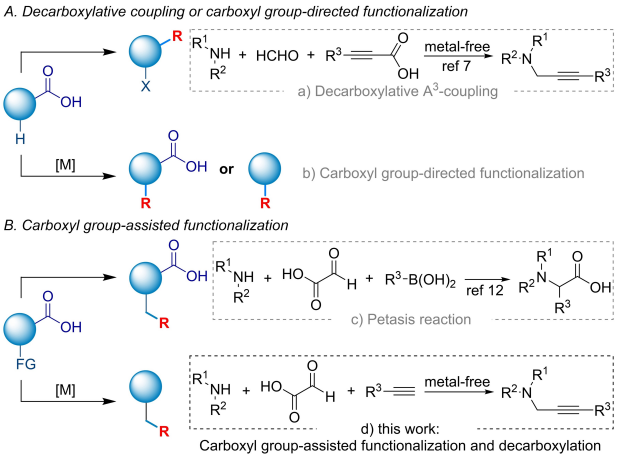
Readily available propargylamines are not only fundamental building blocks in organic synthesis, but also possess many prominent biological activities. A highly efficient, concise and environmentally benign decarboxylative reaction of glyoxylic acid monohydrate with secondary amines and alkynes has been elaborated, and a variety of propargylamines are delivered in moderate to good yields under metal-free conditions. A mechanism involving a carboxyl group that assists the reactivity of alkynes, which makes the procedure of Michael addition proceeded smoothly, has been proposed.

Propargylamine is a versatile synthon in organic chemistry that has been extensively employed in the construction of heterocycles[1,2] and natural products.[3] Meanwhile, propargylamine frameworks which are of important structural subunits in natural products and functional molecules have unique biological activities.[4] Recently, transition-metal-catalyzed decarboxylative coupling reactions have emerged as powerful methods for the building of propargylamine derivatives due to the advantages associated with the environmental-friendly (releasing nontoxic CO_2) and operational simplicity.[5] Further, the metal-free decarboxylative coupling is also an attractive alternative for forming propargylamines as it makes the process concise and flexible,[6] avoiding metallic residues in the final products. For example, Lee and co-workers reported an intriguing protocol for the generation of propargylamines by metal-free decarboxylative coupling of amines, formaldehyde, and propiolic acids (Scheme 1a).[7] Later on, our group and Kumar's group independently developed the metal- or catalyst-free decarboxylation of propiolic acids to access propargylamines.[8] However, an obvious drawback of these approaches is the requisite of expensive or non-commercial propiolic acids, which typically results in poor step- and cost-efficiency. Hence, it is evident that it is still necessary to develop



Scheme 1. Functionalization of carboxylic acid.

an alternative metal-free decarboxylative access to give propargylamines using readily available starting materials.

Despite the remarkable achievements that have been made in the decarboxylative coupling[9] and carboxyl group-directed functionalization of carboxylic acids[10] (Scheme 1A), the available routes for enhancing the reactivity of the reaction through a carboxyl group-assisted process are still underdeveloped.[11] Among them, the well-known report is the multicomponent Petasis reaction of a glyoxylic acid, an amine, and a boronic acid where the carboxyl group can activate the boronic acid followed by the migration of boronate substituent (Scheme 1c).[12] Meanwhile, glyoxylic acid has been exploited for the synthesis of 3-amino-1,4-enynes[13a] and polysubstituted butenolides[13b] through transition-metal-catalyzed tandem glyoxylic acid-amine-alkyne coupling process. These studies led us to think about whether glyoxylic acid can enhance the reactivity of alkynes with *in situ* formed iminium ion owing to its distinctive chemical properties such as electron-withdrawing effect and removability. However, some challenges remain: (1) the activation of alkyne substrates under metal- and base-free conditions, and (2) the control of the decarboxylation process which may shut down the reactivity if it conducts in the beginning.[14] Herein, we report a carboxyl group-assisted metal-free decarboxylative transformation of glyoxylic acid, amines, and alkynes into propargylamines where glyoxylic acid plays a key role in the assembly of the reaction (Scheme 1d).

We commenced our investigation by conducting the model reaction of *N*-methylbenzylamine **1a**, glyoxylic acid monohydrate **2a**, and ethynylbenzene **3a**. Initially, we examined the reaction at 80 °C for 12 hours in acetonitrile (MeCN) without any

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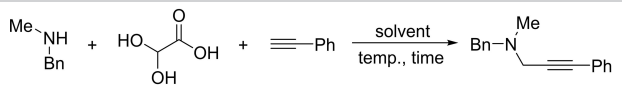
metal catalyst, and a 62% yield of desired product **4a** was observed (Table 1, entry 1). Subsequently, a series of solvents, including toluene, tetrahydrofuran (THF), dioxane, 1,2-dichloroethane (DCE), DMF, and ethanol, were evaluated (entries 2–7). These results indicated that the yields were significantly improved in DCE (entry 4) and slightly increased in toluene (entry 2), respectively. Nevertheless, others delivered propargylamine **4a** in a poor yield. After that, further investigations were performed using DCE as the solvent. When the amount of substrate **3a** was changed (entries 8 and 9), the corresponding yield decreased to 61% and 71%, respectively. Concerning the decarboxylative process, heating to 95 °C resulted in an increase of the yield from 78% to 86% (entry 10). A lower temperature (60 °C) did not facilitate this transformation (entry 11), which is similar to the metal-free A^3-coupling.[7,8c] These results indicated that higher temperature was essential for the reaction. No amelioration was observed when prolonging or shortening the reaction time, providing **4a** in 75% and 66% yield, respectively (entries 12 and 13).

With the optimized conditions established, the substrate scope of amines **1** and alkynes **3** was tested by decarboxylative coupling of glyoxylic acid monohydrate (Scheme 2). First, different amines **1** were examined. In general, the increase of steric bulk on the amine substrate leads to higher reaction yields maybe due to the intermediate **5** formed from the sterically hindered amine is more stable (see Scheme 3 proposed mechanism). As expected, all *N*-alkyl substituted benzylamines could be employed and afforded the corresponding compounds **4a**–**4f** in high yields except the product **4c**. For example, *N*-*tert*-butyl benzylamines with both electron-donating and -withdrawing groups on the phenyl moiety were well tolerated and yielded the desired **4e** and **4f** in 93% and 78% yields, respectively. Additionally, secondary aliphatic amines reacted smoothly to provide the desired propargylamines **4g**–**4j** in 54–79% yields. However, when the cyclic and primary amines were used, only the morpholine could produce a poor yield of the target product **4k**. Next, we investigated the scope of alkynes **3**. Phenylacetylenes with electron-donating substituents (methyl, *t*-butyl, methoxy) and electron-neutral substituent (phenyl) formed the desired products **4o**, **4p**, **4r**, and **4s** in good yields; when the 1-butyl-4-ethynylbenzene was used, the reaction gave lower yield (**4q**, 39% yield). Similarly, the phenylacetylenes with electron-withdrawing groups (chloro, fluoro, trifluoromethyl) gave the desired products **4t**–**4w** in 65–69% yields. To our satisfaction, the aliphatic alkynes were also tolerated well in the reaction and gave the target products **4x**

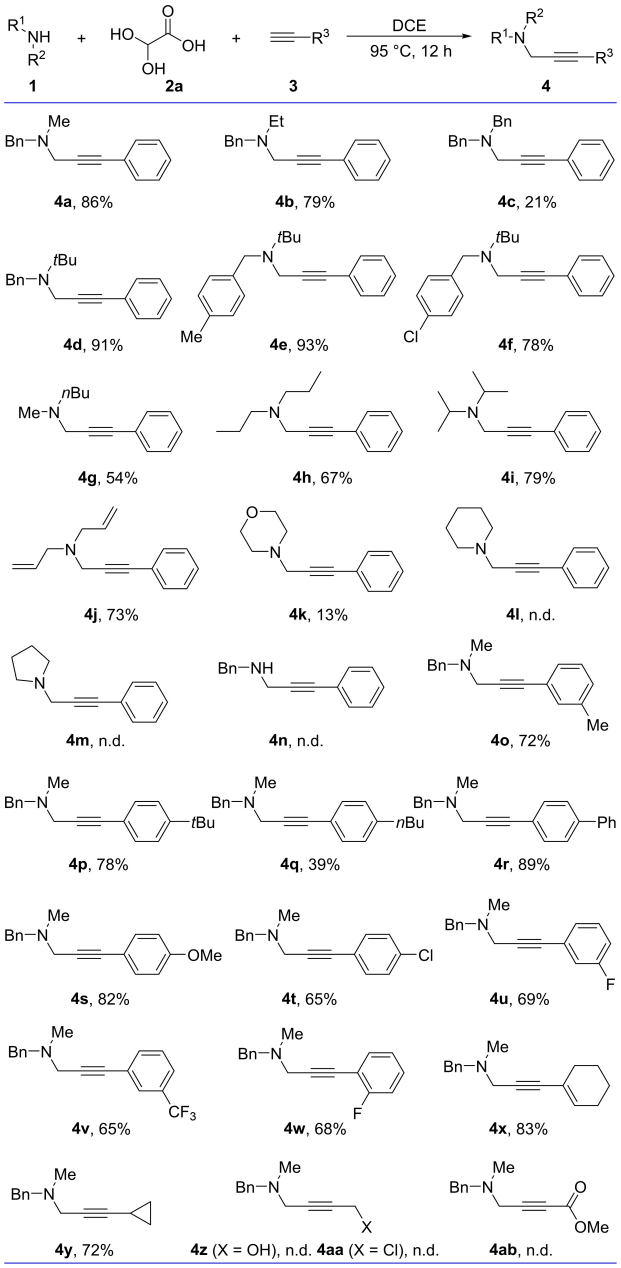
Table 1. Optimization of the reaction conditions.[a]



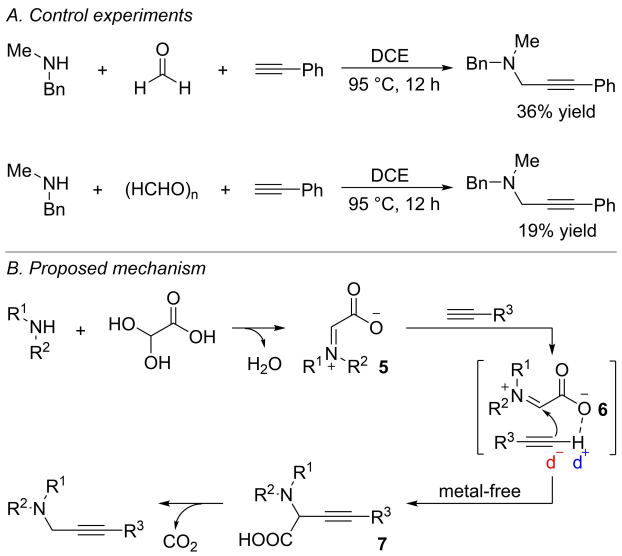
1a **2a** **3a** **4a**

Entry	Ratio of **1a**:**2a**:**3a**	Solvent	Temp. [°C]	Yield[b] [%]
1	1.0:1.2:1.2	MeCN	80	62
2	1.0:1.2:1.2	toluene	80	68
3	1.0:1.2:1.2	THF	80	25
4	1.0:1.2:1.2	DCE	80	78
5	1.0:1.2:1.2	dioxane	80	13
6	1.0:1.2:1.2	DMF	80	27
7	1.0:1.2:1.2	EtOH	80	54
8	1.0:1.2:0.8	DCE	80	61
9	1.0:1.2:1.4	DCE	80	71
10	1.0:1.2:1.2	DCE	95	86
11	1.0:1.2:1.2	DCE	60	8
12[c]	1.0:1.2:1.2	DCE	95	75
13[d]	1.0:1.2:1.2	DCE	95	66

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.30 mmol), **3a** (0.20 mmol–0.35 mmol) were added to solvent (0.5 mL), and the solution was kept at 60–95 °C for 12 h under atmospheric condition. [b] Isolated yield based on **1a**. [c] 24 h instead of 12 h. [d] 4 h instead of 12 h.



Scheme 2. Scope of amines **1** and alkynes **3**. Reaction conditions: **1** (0.25 mmol), **2a** (0.30 mmol), **3** (0.30 mmol) were added to DCE (0.5 mL), and the solution was kept at 95 °C for 12 h under atmospheric condition. Isolated yield based on amine. n.d. = not determined.



Scheme 3. Mechanistic studies.

and **4y** in good yields. However, on using alkynes with the functionalized group such as prop-2-yn-1-ol, 3-chloroprop-1-yne and methyl propiolate, the desired products **4z**–**4ab** could not be detected.

Based on experimental results and previous reports,[15] a rational pathway is considered (Scheme 3). Initially, the glyoxylic acid monohydrate could undergo condensation with amine forming iminium salt species **5**. Subsequently, the carboxyl group-assisted process presumably not only delivers unusual deprotonation of the alkyne to activate the sp carbon, but also produces the coupled product **7** in the subsequent Michael addition through an unstable intermediate **6**. Control experiments, using the formaldehyde solution or paraformaldehyde instead of glyoxylic acid monohydrate under standard conditions (Scheme 3A), show that the metal-free addition of alkyne to *in situ* formed iminium ion is uncommonly.[2b,7] Further conversion of **7** results in the generation of the desired propargylamine by metal-free decarboxylation.

In conclusion, we have described highly efficient metal-free decarboxylative coupling of glyoxylic acid monohydrate with amines and alkynes to produce propargylamines in moderate to good yields. The results demonstrated that the carboxyl group can enhance the activation of the alkynes to react with iminium ion intermediate without any catalysts loading, thus increasing the sustainability of the process. Development of additional reactions that exploit the decarboxylation process for the functionalization of the intermediate is in progress.

Experimental Section

General procedure: Under atmosphere, a 10 mL reaction tube was charged with the corresponding amine **1** (0.25 mmol, 1.0 equiv.), glyoxylic acid monohydrate **2a** (0.30 mmol, 1.2 equiv.), alkyne **3** (0.30 mmol, 1.2 equiv.) and DCE (0.5 mL), then sealed. Subsequently, the reaction mixture was stirred at 95 °C for 12 h. Afterwards, the reaction system was directly purified by running silica gel flash column chromatography (5–10% ethyl acetate in petroleum ether) to afford the desired products **4a**–**4y**.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: A^3-coupling · Decarboxylation · Metal-free reaction · Multicomponent reaction · Propargylamine

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