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Copper-Catalyzed Highly Efficient Multicomponent Reactions of Terminal Alkynes, Acid Chlorides, and Carbodiimides: Synthesis of Functionalized Propiolamidine Derivatives

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Abstract: Functionalized propiolamidine derivatives were prepared in good to excellent yields under very mild conditions *via* a copper-catalyzed multicomponent reaction (MCR) of readily available terminal alkynes, acid chlorides and carbodiimides with the assistance of triethylamine. The mechanism of this MCR is postulated.

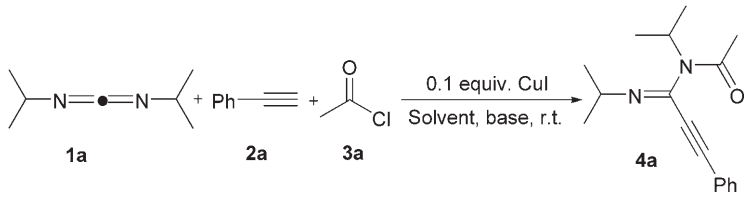
Keywords: acid chlorides; alkynes; carbodiimides; copper; multicomponent reactions; propiolamidine derivatives

Amidine derivatives, due to their unique chemical and structural properties, have received much attention over the past decades and found wide application in medicinal chemistry and synthetic chemistry. Amidine derivatives possessing a wide range of biological and pharmacological activities such as antidegenerative, anticancer, antiplatelet and antimicrobial activities have been reported in the literature.[1] They also act as serine protease inhibitors and nitric oxide synthase inhibitors.[2] On the other hand, substituted amidines are useful intermediates in the synthesis of many heterocyclic compounds[3] and metal complexes.[4] In fact, although various amidines have been reported, little information concerning propiolamidine derivatives could be found in the literature. The catalytic addition of terminal alkynes to carbodiimides by half-sandwich rare earth metal complexes, $LiN(SiMe_3)_2$ or Ru clusters to give the propiolamidine derivatives was published in the past years.[5] Use of acetyllithium as a stoichiometric nucleophilic reagent was employed for the synthesis of propiolamidines, however, the yields were very low.[6] Upon checking the literature, there was no report about the synthesis of *N*-carbonylpropiolamidine derivatives. From these points of view, the search for a synthesis of different types of propiolamidine derivatives is still in demand.

The MCR (multicomponent reaction), offering an efficient route to generate complex molecular frameworks from simple and readily available substrates, is a powerful tool in modern organic synthesis as well as in the fields of combinatorial chemistry and drug discovery.[7] Although little attention was paid to novel MCRs in the second half of the last century, they have naturally been developed as a rapidly evolving research area and have attracted the attention of both academic and industrial scientists in the last few years. Among them, the transition metal-catalyzed MCRs are of high importance since they have excellent catalytic efficiency in most cases.[8] Recently we developed an MCR of terminal alkynes, sulfonyl azides and carbodiimides for the synthesis of functionalized 2-(sulfonylimino)-4-(alkylimino)azetidine derivatives with copper(I) iodide as a catalyst.[9,10] Herein we report a novel copper-catalyzed three-component reaction between terminal alkynes, acid chlorides and carbodiimides to give functionalized propiolamidine derivatives in good to excellent yields.

At first, *N*,*N*′-diisopropylcarbodiimide **1a**, phenylacetylene **2a** and acetyl chloride **3a** were selected as the model substrates (Table 1). Catalyzed by CuI, several bases and solvents were examined to set up a standard set of reaction conditions. When the reaction was performed in CH_2Cl_2 in the presence of 2 equivalents of triethylamine at room temperature for 2 h, it was found that the desired product **4a** was indeed obtained albeit in only 40% yield (Table 1, entry 1). Yields of the desired product can be improved to 66% when $CHCl_3$ or diethyl ether was used as the solvent (Table 1, entries 2 and 3). Toluene was not a

Table 1. CuI-catalyzed the three-component reaction of *N,N′*-diisopropylcarbodiimide, phenylacetylene and acetyl chloride.



1a 2a 3a 4a

Entry	Solvent	Base	Time [h]	Yield [%][a,b]
1	CH_2Cl_2	TEA[c]	2	40
2	$CHCl_3$	TEA	2.5	66
3	ether[d]	TEA	5	66
4	toluene	TEA	4	44
5	THF	TEA	4	78
6	CH_3CN	TEA	2	81
7	CH_3CN	TEA	6	80
8	CH_3CN	K_2CO_3	2	33
9	CH_3CN	pyridine	2	18
10	CH_3CN	DMAP	2	<5

[a] *N,N′*-Diisopropylcarbodiimide (1 mmol), phenylacetylene (1.2 mmol), acetyl chloride (1.2 mmol), base (2 mmol), and CuI (0.1 mmol) in solvent (3 mL) for the indicated time at room temperature under a nitrogen atmosphere.
[b] Isolated yields based on *N,N′*-diisopropylcarbodiimide.
[c] Triethylamine.
[d] Diethyl ether.

good choice here (Table 1, entry 4). It is encouraging to find that the result was further improved using THF as solvent (Table 1, entry 5). However, an even better result came from the use of CH_3CN in the presence of triethylamine and **4a** was obtained in 81% yield (Table 1, entry 6). Prolonging the reaction time (6 h) or use of 2 equivalents of pyridine, DMAP or K_2CO_3 instead of triethylamine as the bases could not improve the result (Table 1, entries 7–10).

It can be summarized from Table 1 that the combination of CuI, TEA and CH_3CN was a most efficient catalytic system to catalyze the MCR of *N,N′*-diisopropylcarbodiimide, phenylacetylene and acetyl chloride. To explore the scope of this catalytic system, a variety of substrates was applied and the results are shown in Table 2.

Benzoyl chloride gave the corresponding functionalized propiolamidine derivatives in good to excellent yields. Aliphatic acid chlorides, such as acetyl chloride, propionyl chloride and phenoxyacetyl chloride were also appropriate substrates. As far as the alkynes were concerned, aromatic alkynes substituted at the phenyl ring with Br, Me, Pr, Bu and MeO were all converted into the corresponding products efficiently, indicating no remarkable electronic effects in the reaction. It is noteworthy that 1-hexyne and 1-heptyne, two aliphatic alkynes, afforded the desired products in good yields as well. Two kinds of carbodiimides, DCC or DIC, can be used successfully for this reaction. Nevertheless, when *N,N′*-diphenylcarbodiimide or *N*-phenyl-*N′*-*n*-butylcarbodiimide was used as the substrate, almost no corresponding product was obtained. The failure may be ascribed to the weak nucleophilicity of nitrogens which were conjugated with a benzene ring.

According to previous work[11,12] and on the basis of the above results, a tentative mechanism is suggested in Scheme 1. The carbodiimide **1** reacts with acid chloride **3** to form *N*-acyliminium salt **5**, and alkyne **2** is immediately converted to the copper acetylide **4** in the presence of triethylamine with one equivalent of triethylamine acid salts being released. Then the nucleophilic attack of **4** on **5** gives the desired product **6** and liberates the copper catalyst to complete the catalytic cycle.

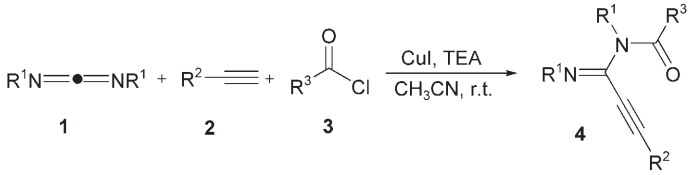
In conclusion, we have developed a copper-catalyzed multicomponent coupling of carbodiimides, alkynes, and acid chlorides. This MCR provides an efficient method to construct functionalized propiolamidine derivatives.

Experimental Section

General Procedure for the Synthesis of Functionalized Propiolamidine Derivatives

A suspension of carbodiimide (1.0 mmol) and acid chloride (1.2 mmol) was stirred for 10 min in a 10-mL two-necked vial under a nitrogen atmosphere, using tap water to cool the reaction vial. Then anhydrous acetonitrile (3 mL), triethylamine (0.28 mL, 2.0 mmol), CuI (19 mg, 0.1 mmol) and alkyne (1.2 mmol) were added successively at room temper-

Table 2. CuI-catalyzed synthesis of functionalized propiolamidine derivatives **4**.

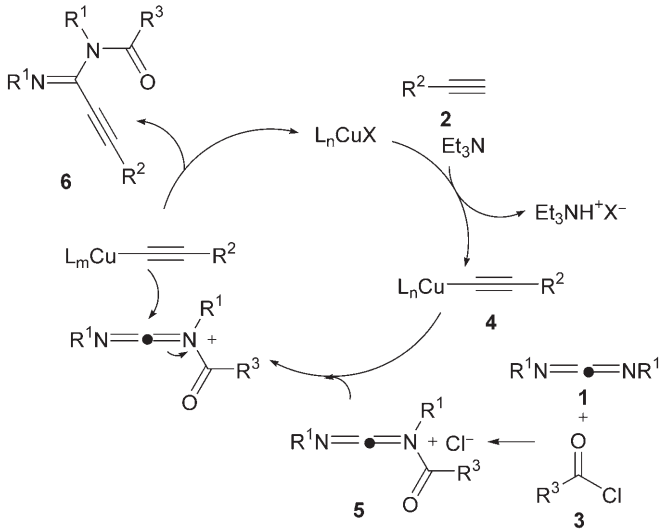


1 2 3 4

Entry	R^1	R^2	R^3	Time [h]	Yield [%][a,b]
1	*i*-Pr	Ph	CH_3	2	81, **4a**
2	*i*-Pr	4-$CH_3OC_6H_4$	CH_3	2	90, **4b**
3	*i*-Pr	Ph	CH_3CH_2	2	96, **4c**
4	*i*-Pr	Ph	$PhOCH_2$	2	53, **4d**
5	*i*-Pr	$CH_3(CH_2)_4$	CH_3	4	72, **4e**
6	*i*-Pr	4-$CH_3C_6H_4$	CH_3	2	95, **4f**
7	*i*-Pr	4-BrC_6H_4	CH_3	2	83, **4g**
8	*i*-Pr	$CH_3(CH_2)_3$	CH_3	2	60, **4h**
9	*i*-Pr	4-$CH_3OC_6H_4$	Ph	2	80, **4i**
10	*i*-Pr	4-*n*-PrC_6H_4	CH_3	2	79, **4j**
11	*i*-Pr	Ph	Ph	2	75, **4k**
12	cyclohexyl	Ph	CH_3	2	71, **4l**
13	cyclohexyl	4-$CH_3OC_6H_4$	Ph	2	78, **4m**
14	cyclohexyl	4-*n*-BuC_6H_4	Ph	2	83, **4n**
15	cyclohexyl	$CH_3(CH_2)_3$	CH_3CH_2	3	66, **4o**
16	cyclohexyl	Ph	$PhOCH_2$	2	61, **4p**

[a] *N,N′*-Dialkylcarbodiimide (1 mmol), alkyne (1.2 mmol), acid chloride (1.2 mmol), TEA (2 mmol), and CuI (0.1 mmol) in CH_3CN (3 mL) for the indicated time at room temperature under nitrogen atmosphere.

[b] Isolated yields based on *N,N′*-dialkylcarbodiimides.



Scheme 1.

ature. The mixture was stirred for the indicated time in Table 2 (detected by TLC). To the resultant mixture was added water (15 mL) and the whole was extracted with CH_2Cl_2 (3×30 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution and then water. Then it was dried over anhydrous $MgSO_4$ and evaporated under vacuum. The residue was purified on a silica gel column with petroleum ether/ethyl acetate as eluent to give the corresponding functionalized propiolamidine derivatives. For more details, see Supporting Information.

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