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Effective Synthesis of Benzyl 3-Phenylpropiolates Via Copper(I)-Catalyzed Esterification of Alkynoic Acids with Benzyl Halides Under Ligand-Free Conditions

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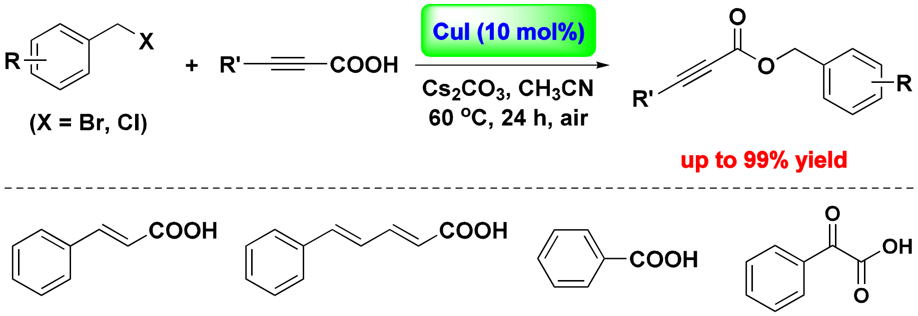
Abstract We developed an efficient way to prepare benzyl 3-phenylpropiolates via copper-catalyzed coupling between corresponding benzyl halides and alkynoic acids under ligand-free condition. This methodology is also suitable for aromatic and *α*,*β*-unsaturated acids. The desired esters could be obtained in good yields.

Graphical Abstract We developed an efficient way to prepare benzyl 3-phenylpropiolates via copper-catalyzed coupling between corresponding benzyl halides and alkynoic acids under ligand-free condition. This methodology is also suitable for aromatic and cinnamic acids. The desired esters could be obtained in good yields.



Keywords Esterification reactions · Benzyl halides · Carboxylic acids · Ligand-free · Benzyl 3-phenylpropiolate

1 Introduction

As we know that esterification which is one of the most useful synthetic transformations has attracted great attentions [1]. Moreover, alkyl esterification is also an usual approach to protect carboxyl group in the total synthesis. Among alkyl esterbenzyl esters were more stable under acidic and basic conditions and generally cleaved under catalytic hydrogenolysis [2, 3]. Furthermore, benzyl 3-phenylpropiolates are important building blocks of heterocycles [4–10], so that many researchers devote themselves to investigating alternative methods to synthesize them (Fig. 1) [11–14]. Not long ago, Coleman and co-workers reported phase-transfer esterification of carboxylic acids. But unsaturated acids only afforded the desired esters in moderate yields [15].

In the past several years, most methods for esterification were developed [16–27]. For example, copper-catalyzed oxidative or direct esterification was found to be an effective approach by Patel and co-workers [16–23]. In

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addition, ionic liquid was employed as the solvent, which has many advantages, such as low volatility, good thermal stability [24–27]. However, ionic liquid needs to be prepared exclusively and some kinds of ionic liquid are moisture sensitive. A simpler, wider and more practical way in industrial chemicals synthesis is always highly appreciated. Transition metal catalysts can activate many reactions under mild conditions. Among these transition metal catalysts, copper salts are ideal catalysts and extensively used in chemical industry due to their readily available, cheap and environmental friendly characters [28–31]. In recent years, our group have made many efforts on copper-catalyzed coupling reactions [32, 33]. These coupling reactions effectively construct C–C and C–N bond. Lately, we have reported an example of highly effective synthesis of methyl esters from benzylic alcohols, aldehydes and acids via copper-catalyzed C–C cleavage from tert-butyl hydroperoxide [34]. It arouses our great interest in studying esterifications. In continuation of our research of copper-catalyzed esterification, herein, we report an efficient approach to synthesize unsaturated benzyl esters from phenylpropiolic acids catalyzed by copper(I).

2 Experimental

2.1 General Information

All reactions were carried out under air. Solvents were dried and degassed by standard methods. All of the benzyl halides and carboxylic acids are readily available. Flash column chromatography was performed using silica gel (300–400 mesh). Analytical thin-layer chromatography was performed using glass plates pre-coated with 200–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). NMR spectra were measured in $CDCl_3$ on a Varian Inova-400 NMR spectrometer (400 or 300 MHz) with TMS as an internal reference. Products were characterized by comparison of ^1H NMR, ^{13}C NMR and TOF–MS data in the literature.

2.2 General Procedure for Esterification of Benzyl Halide and Alkynoic Acid

A mixture of benzyl halide (0.4 mmol), alkynoic acid (0.6 mmol), Cs_2CO_3 (2 equiv), CuI (10 mol%), and CH_3CN (2 mL) in a tube was stirred in air at 60 °C for 24 h. After that

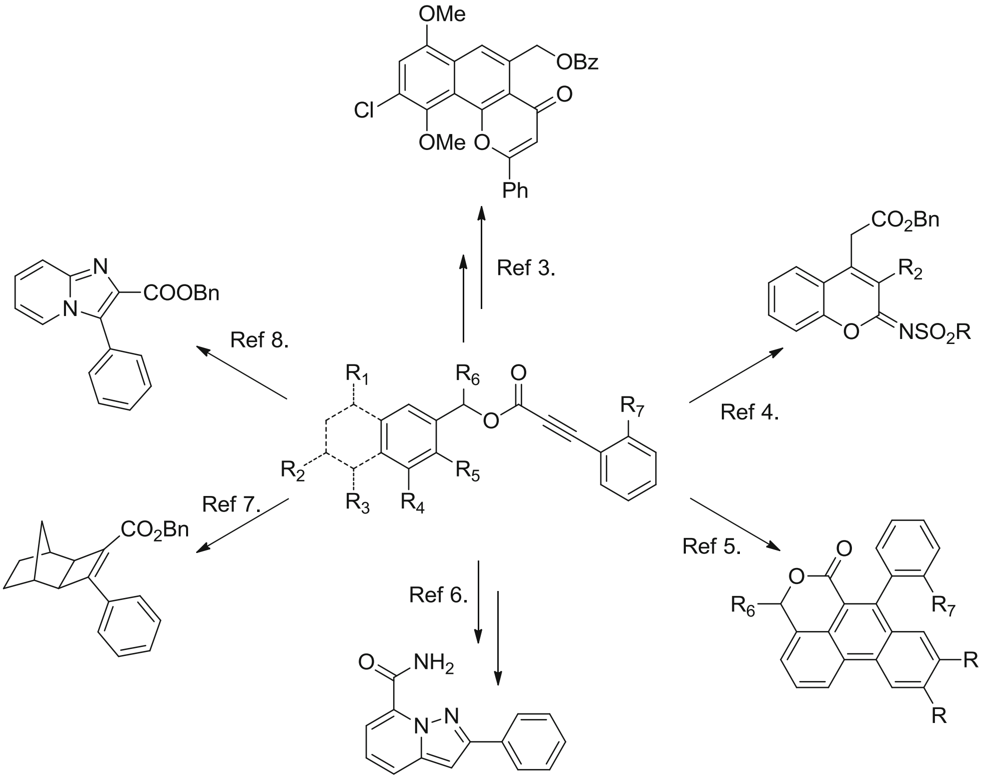


Fig. 1 Preparation of some useful compounds from benzyl 3-phenylpropiolates

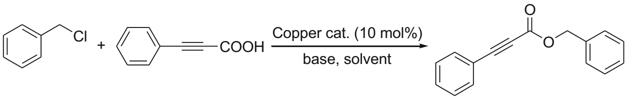
the mixture was poured into ethyl acetate, then washed with water, extracted with ethyl acetate, dried by anhydrous Na_2SO_4, then filtered and evaporated under vacuum, the residue was purified by flash column chromatography (petroleum ether or petroleum ether/ethyl acetate) to afford the corresponding coupling products. The characterization of the corresponding products was shown in Supporting Materials.

3 Results and Discussions

We initiated our studies by investigating the reaction of benzyl chloride with phenylpropiolic acid. In the presence of 10 mol% copper iodide and 2 equivalents potassium carbonate in the acetonitrile at 30 °C, benzyl 3-phenylpropiolate was obtained in 11 % yield (Table 1, entry 1). Temperature influenced the reaction obviously. Elevating the reaction temperature to 60 °C, a big improvement in the reaction yield was obtained (entry 2). Several solvents were examined next. As a result, acetonitrile showed uniquely good acceleration to the reaction (entries 4–8). Besides, reactions carried out with carbonates as bases gave remarkably higher yield than any other bases did (entry 2 vs. entries 9–14). Especially when cesium carbonate was employed as the base, almost quantitative ester was obtained (entry 9). We also probed various commercially available copper salts and copper powder (entries 14–18), and copper (I) iodide was proved as the best catalyst (entry 19). Furthermore, reagents containing iodine were screened, including tetramethylammoniumiodide (TMAI), tetrabutylammoniumiodide (TMBI), iodine, NaI, KI and iodobenzene diacetate. It can be seen that moderate yields of desired ester were acquired (entries 19–24). Blank experiment exhibited that no copper (I) catalyst was added, nearly no reaction could occur (entry 25). Varying the amount of catalyst or base was not favorable for the catalytic reaction (entries 26–28). Finally, we used copper iodide (99.999 %) instead of analytically pure copper iodide, and the same yield was got (entry 29).

With the optimized conditions in hand, we further expanded this copper-catalyzed esterification to a wide range of substrates. In the course of experiments, excessive phenylpropiolic acid was found to give better results. As summarized in Table 2, whether the phenyl ring of benzyl chlorides with electron-withdrawing group or electron-donating group were investigated, the corresponding products were acquired in excellent yields (Table 2, entries 2–5). We also examined various phenylpropiolic acids. It can be seen that *para*-substituted phenylpropiolic acids gave moderate yields, whereas *meta*- as well as *ortho*-substituted phenylpropiolic acids gave the corresponding products in good yields (entries 6–10). In order to broaden this methodology, various benzyl bromides and carboxylic acids were investigated subsequently. Reactions of phenylpropiolic acid with benzyl bromide bearing different substituents occurred in good to excellent yields (entries 11–16). Generally, the benzyl halides with electron-withdrawing groups afforded better results than those with electron-donating groups. Unfortunately, aliphatic propiolic acid was unreactive under the same conditions (entry

Table 1 Screening various conditions for copper-catalyzed reaction between benzylic chloride and phenylpropiolic acid



Entry	Copper cat.	Base	Solvent	T (°C)/t (h)	Yield (%)[a]
1	CuI	K_2CO_3	MeCN	30/24	11
2	CuI	K_2CO_3	MeCN	60/24	70
3	CuI	K_2CO_3	MeCN	60/12	44
4	CuI	K_2CO_3	DMF	60/24	NR
5	CuI	K_2CO_3	DMSO	60/24	13.1
6	CuI	K_2CO_3	Dioxane	60/24	NR
7	CuI	K_2CO_3	Toluene	60/24	NR
8	CuI	K_2CO_3	PEG-400	60/24	13
9	CuI	Cs_2CO_3	MeCN	60/24	>99
10	CuI	K_3PO_4	MeCN	60/24	45
11	CuI	^{t}BuOK	MeCN	60/24	56
12	CuI	CsF	MeCN	60/24	11
13	CuI	Et_3N	MeCN	60/24	NR
14	CuI	DBU	MeCN	60/24	46
15	CuCl	Cs_2CO_3	MeCN	60/24	53
16	CuBr	Cs_2CO_3	MeCN	60/24	39
17	$Cu(OAc)_2$	Cs_2CO_3	MeCN	60/24	43
18	Cu powder	Cs_2CO_3	MeCN	60/24	34
19	TMAI	Cs_2CO_3	MeCN	60/24	79
20	TBAI	Cs_2CO_3	MeCN	60/24	30
21	I_2	Cs_2CO_3	MeCN	60/24	82
22	NaI	Cs_2CO_3	MeCN	60/24	82
23	KI	Cs_2CO_3	MeCN	60/24	83
24	$PhI(OAc)_2$	Cs_2CO_3	MeCN	60/24	54
25	–	Cs_2CO_3	MeCN	60/24	trace
26	CuI	Cs_2CO_3	MeCN	40/24	61
27[b]	CuI	Cs_2CO_3	MeCN	40/24	73
28[c]	CuI	Cs_2CO_3	MeCN	40/24	24
29[d]	CuI	Cs_2CO_3	MeCN	60/24	>99

Reaction conditions: Benzyl chloride (0.3 mmol), phenylpropiolic acid (0.3 mmol), copper catalyst (10 mol%), base (2 equiv), solvent (2 mL), 30–60 °C, 24 h, air

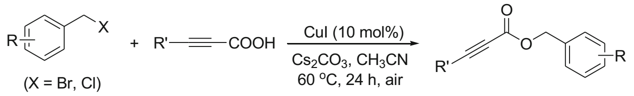
[a] GC-yield based on phenylpropiolic acid (n-decane)

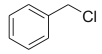
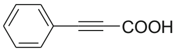
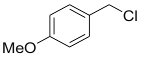
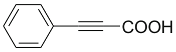
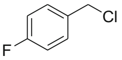
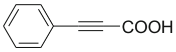
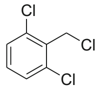
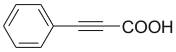
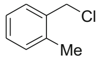
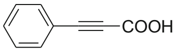
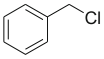
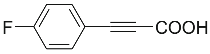
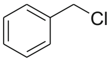
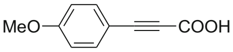
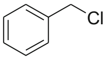
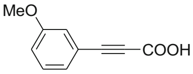
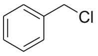
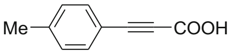
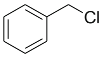
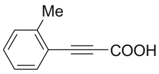
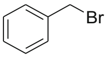
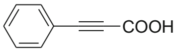
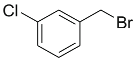
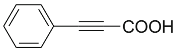
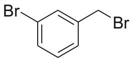
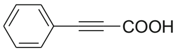
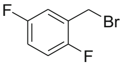
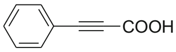
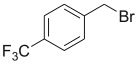
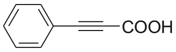
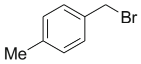
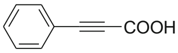
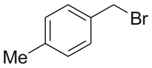
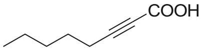
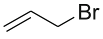
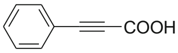
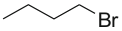
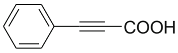
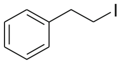
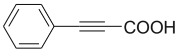
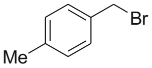
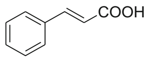
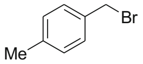
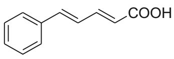
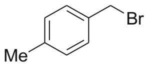
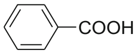
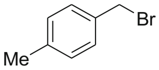
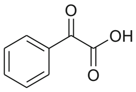
[b] CuI (5 mol%)

[c] Cs_2CO_3 (1 equiv)

[d] CuI (99.999 %) from Aldrich was employed

Table 2 CuI-catalyzed esterification of benzyl halide and alkynoic acid



Entry	Benzyl halide	Alkynoic acid	Yield (%)[a]
1			99
2			90
3			87
4			92
5			90
6			55
7			65
8			79
9			64
10			84
11			99
12			78
13			87
14			76
15			79
16			93
17			NR
18			77
19			72
20			66(34[b])
21			99
22			99
23			99
24			34

Reaction conditions: Benzyl halide (0.4 mmol), alkynoic acid (0.6 mmol), CuI (10 mol%), Cs_2CO_3 (2 equiv), CH_3CN (2 mL), 60 °C, 24 h, air

[a] Isolated yield based on benzyl halide

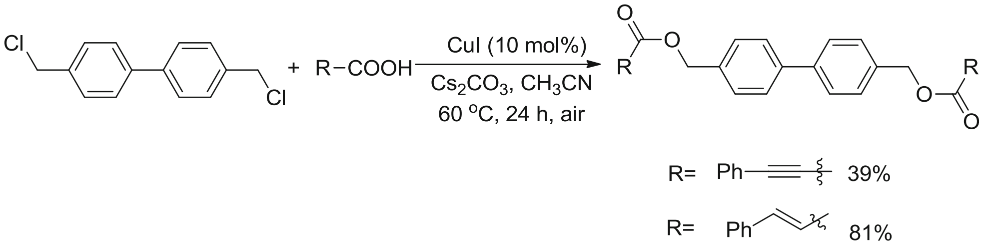
[b] In the absence of CuI

17). However, aliphatic bromides such as allyl bromide and butyl bromide and (2-iodoethyl) benzene proved to be suitable substrates (entries 18–20). For the (2-iodoethyl) benzene as the substrate, the control experiment was performed in the absence of CuI. It can be seen that only 34 % yield of the corresponding ester could be obtained (entry 20). This could show the high catalytic effect of CuI for this reaction. Interestingly, cinnamic acid, cinnamal acetic acid and benzoic acid could offer the corresponding esterified products in excellent yields (entries 21–23), while benzoyl formic acid gave the desired product within poor yield (entry 24).

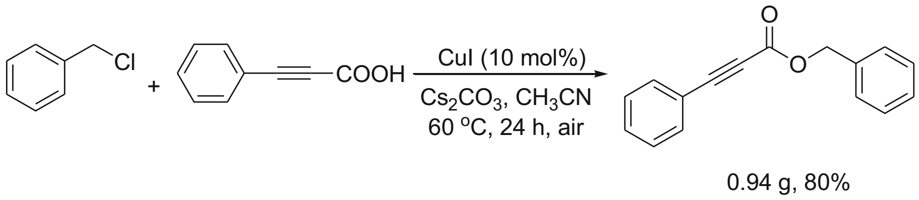
Gratifyingly, the esterification of phenylpropiolic acids and cinnamic acid to 4,4′-bis(chloromethyl)-1,1′-biphenyl was performed to access the corresponding diesterified products in 39 and 81 %, respectively (Scheme 1). We were also pleased to find that 0.94 g of benzyl 3-phenylpropiolate was obtained when 5 mmol benzyl chloride was reacted with phenylpropiolic acid under the optimized conditions (Scheme 2). It can be seen that this methodology provided an alternative and practical way to synthesize benzyl esters. Finally we studied the reactivity of alkenyl halide and phenyl halide. Unfortunately, they did not proceed at all under these conditions (Scheme 3).

To get more information of the mechanism, the reaction of benzyl chloride with phenylpropiolic acid was carried out at 60 and 100 °C without copper iodide, respectively (Scheme 4). As we expected, electrophilic esterification reluctantly happened at the higher temperature whereas it hardly occurred at the lower temperature. A proposed mechanism based on previous studies is shown in Scheme 5. Two possible catalytic cycles may be involved in this reaction. Firstly, copper iodide is coordinated with acetonitrile to form L_3CuI. Then substitution of L_3CuI by a phenylpropiolic acid generates cupric phenylpropiolate complex **I** (in path **A**) or L_3CuI inserts to C–Cl bond to afford intermediate **II** (in path **B**). Subsequently, intermediate **III** is smoothly generated by the working of intermediate **I** with benzyl chloride or by the working of intermediate **II** with phenylpropiolic acid [16, 35]. Finally, reductive elimination of intermediate **III** regenerates L_3CuI and give benzyl 3-phenylpropiolate. Certainly, during the reaction, it is believed that using catalytic amount of CuI,

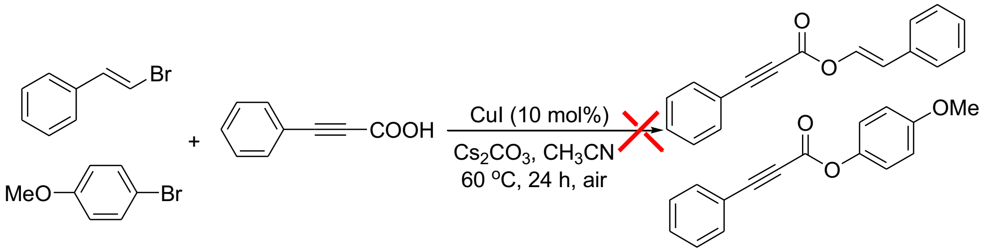
Scheme 1 Diesterifications of 4,4′-bis(chloromethyl)-1,1′-biphenyl



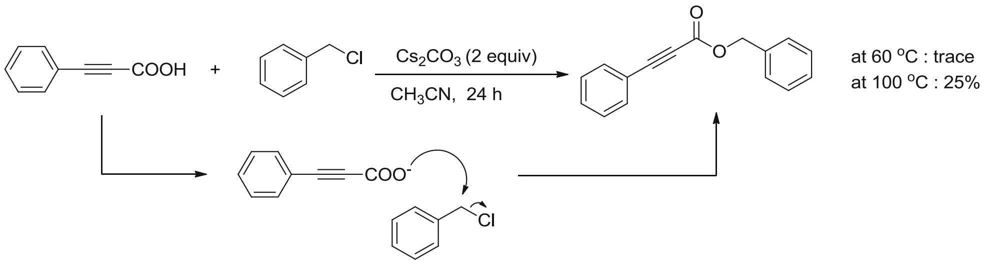
Scheme 2 Benzyl esrerification of phenylpropiolic acid in a large scale

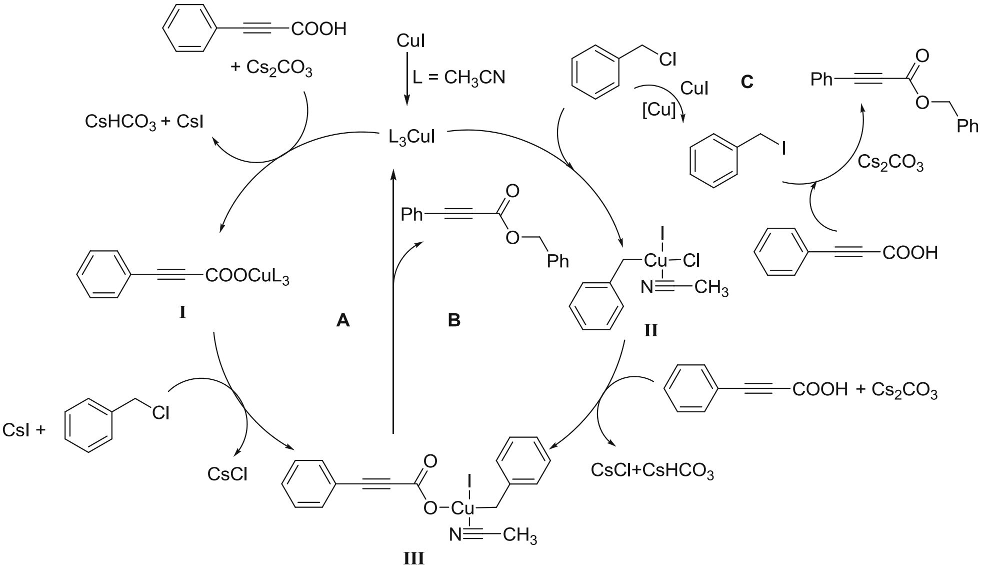


Scheme 3 CuI-catalyzed esterification of alkenyl halide and phenyl halide



Scheme 4 Electrophilic esterification without copper catalyst





Scheme 5 Proposed mechanism of benzyl esterification

benzyl bromide or benzyl chloride could be converted to benzyl iodide to some extent which is a better electrophile towards attach by the carboxylate as shown in path **C**.

4 Conclusions

In summary, we have demonstrated an efficient protocol for the benzyl esterifications of phenylpropiolic acid under mild conditions. Compared with previous methods, the present methodology not only uses simple readily available copper salts as catalyst but also can synthesize benzyl 3-phenylpropiolate in a large scale, which provides potential value in industrial application. We have also developed a way to prepare benzyl benzoate, benzyl cinnamate and benzyl cinnamal acetate. Ongoing efforts to attractive esterification in the synthesis of some biologically active molecules are currently underway in our group.

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