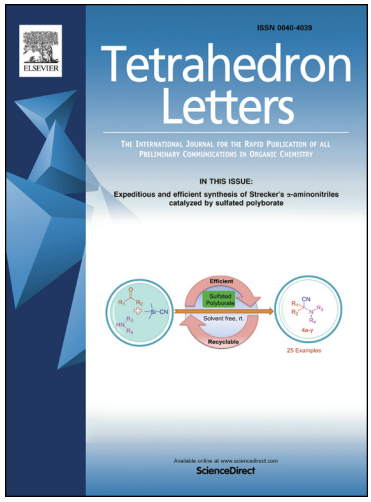


# Copper-Catalyzed Annulation of 2-Bromobenzoic Esters with Terminal Alkynes towards 3-Substituted Isocoumarins

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## Graphical Abstract

**Copper-Catalyzed Annulation of 2-Bromobenzoic Esters with Terminal Alkynes towards 3-Substituted Isocoumarins**

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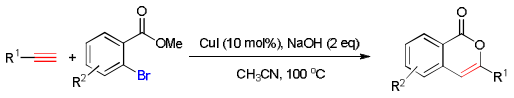


$R^1$ = aryl, alkyl

$R^2$ = H, F, Cl, Br, Me, MeO

- mild conditions
- high yield and regioselectivty
- wide functional group tolerance

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# Copper-Catalyzed Annulation of 2-Bromobenzoic Esters with Terminal Alkynes towards 3-Substituted Isocoumarins

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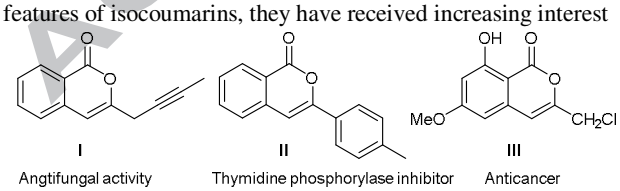
ABSTRACT

An efficient method for the synthesis of 3-substituted isocoumarins that are an important class of biologically active scaffolds via annulation of 2-bromobenzoic esters with terminal alkynes by copper catalyzed is described. The advantages of this method include mild reaction conditions, high yield and regioselectivity, and wide tolerance toward functional groups.



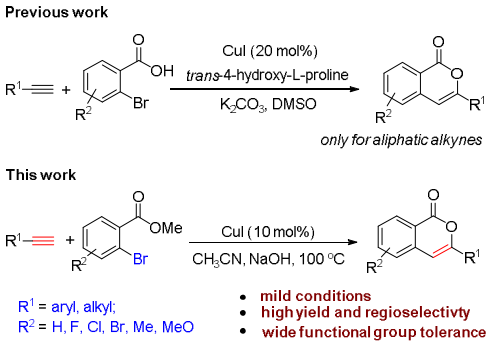
Isocoumarins, especially for 3-substituted isocoumarins, are an important class of biologically active scaffolds, and they are present in a large number of pharmaceuticals and natural products (Scheme 1).[1-3] 3-Substituted isocoumarins are also endowed as pivotal intermediates in the synthesis of natural products, such as canesin, α- and β-sorigenin methyl ethers, and isochromenes as well as some isoquinoline alkaloids.[4]

Traditionally, 3-substituted isocoumarins are synthesized by the transition metal catalysed[5]/Lewis acids mediated[6] *6-endo-dig* cyclization of 2-alkynylbenzoic acid/esters that are pregenerated from 2-halobenzoic acid/esters with terminal alkynes by the Sonogashira-type coupling reaction.[7] One-pot synthesis of these compounds has also been developed via direct Pd-catalyzed Sonogashira-type coupling of terminal alkynes with 2-halobenzoic acids together with the subsequent *6-endo-dig* cyclization.[8] Because of the diverse spectrum of physiochemical features of isocoumarins, they have received increasing interest




**Scheme 1**. Biologically active isocoumarins.

in exploring efficient and straightforward methods for their synthesis.[9,10] Remarkably, the direct *ortho*-C–H activation and oxidative annulation of benzoic acids and their derivatives towards isocoumarins have been successfully developed in recent years.[11,12] However, besides requirement of noble metals such as Pd, Ru, Rh, and Ir, the reactions generally suffer from one or more drawbacks, such as harsh reaction conditions, limited substrate scope, and unsatisfactory yields.




**Scheme 2**. Methods for the synthesis of isocoumarins.

Over the past decades, copper salts have received great attention as inexpensive, readily available and effective

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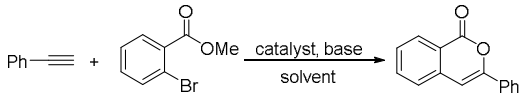
alternatives to noble metals, especially for palladium, in organic synthesis.[13] These features have also inspired organic chemists to develop the copper-catalyzed approaches to isocoumarins.[14-16] In 2009, a copper-catalyzed annulation of 2-iodobenzoic acids with terminal alkynes was explored by Abarbri, Parrain and coworkers, but it gave a mixture of the *6-endo-dig* (isocoumarins) and *5-exo-dig* (phthalides) annulation products.[15a] Recently, Pal and coworkers developed a similar coupling-cyclization reaction with the aid of ultrasound, producing the desired 3-substituted isocoumarins in good to high yields (60–85%).[15b] Although relatively lower yields (38–85%) were observed, Lee and coworkers realized the reaction from 2-iodobenzoic acids and terminal alkynes under copper-catalyzed ultrasound-free conditions.[15c] Notably, more available and less reactive 2-bromobenzoic acids were also employed as substrates by Ma and coworkers for the transformation under CuI/amino acid-catalyzed conditions, but the reaction limits to aliphatic alkynes (Scheme 2).[15d]

Herein, we wish to report a general and highly efficient synthesis of 3-substituted isocoumarins via copper-catalyzed cyclization of 2-bromobenzoic esters with terminal alkynes under mild reaction conditions (Scheme 2). 2-Halobenzoic esters are readily available, however, to the best of our knowledge, only one reaction of methyl 2-iodobenzoate with phenylacetylene is reported, which affords a mixture of the Sonogashira-type coupling (methyl 2-(phenylethynyl)benzoate, 42% yield) and annulation (3-phenylisocoumarin, 53% yield) products.[16]

**Table 1**

Optimization of the reaction conditions[a]




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

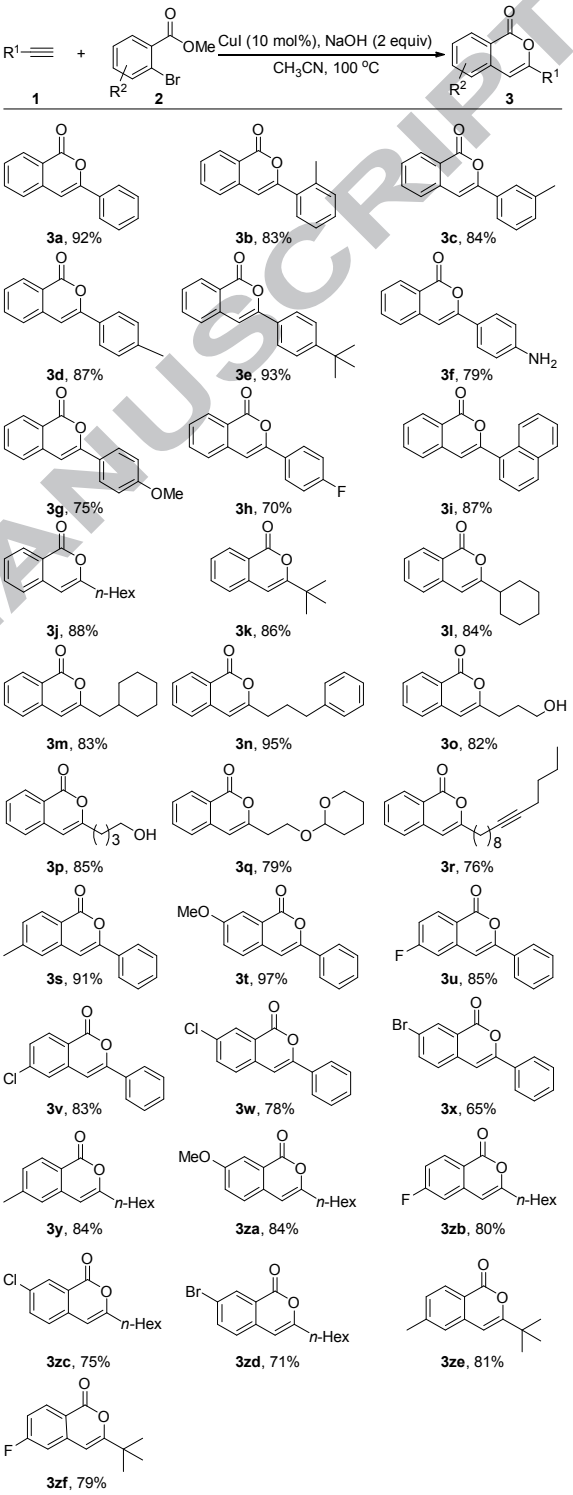
| Entry | Catalyst | Base | Solvent | Yield(%)[b] |
|---|---|---|---|---|
| 1 | CuI | NaOH | DMF | 90 |
| 2 | CuI | none | DMF | N.D.[c] |
| 3 | none | NaOH | DMF | N.D. |
| 4 | CuCl | NaOH | DMF | 62 |
| 5 | CuBr | NaOH | DMF | 36 |
| 6 | CuO | NaOH | DMF | trace |
| 7 | $CuCl_2$ | NaOH | DMF | N.D. |
| 8 | $CuBr_2$ | NaOH | DMF | N.D. |
| 9 | $Cu(OH)_2$ | NaOH | DMF | 18 |
| 10 | CuI | $Et_3N$ | DMF | trace |
| 11 | CuI | $Na_2CO_3$ | DMF | N.D. |
| 12 | CuI | $K_2CO_3$ | DMF | trace |
| 13 | CuI | $Cs_2CO_3$ | DMF | N.D. |
| 14 | CuI | $^t$BuONa | DMF | 29 |
| 15 | CuI | $^t$BuOK | DMF | 35 |
| 16 | CuI | KOH | DMF | 59 |
| 17 | CuI | NaOH | DMSO | 37 |
| 18 | CuI | NaOH | dioxane | 51 |
| 19 | CuI | NaOH | $CH_3CN$ | 92 |
| 20[d] | CuI | NaOH | $CH_3CN$ | 95 |
| 21[e] | CuI | NaOH | $CH_3CN$ | trace |
| 22[f] | CuI | NaOH | $CH_3CN$ | trace |

[a] Reaction conditions: phenylacetylene **1a** (0.2 mmol), methyl 2-bromobenzoate **2a** (0.2 mmol), catalyst (0.02 mmol, 10 mol%), base (0.4 mmol, 2.0 equiv), solvent (1.0 mL), $N_2$, 100 °C, 24 h. [b] GC yield using *n*-dodecane as an internal standard. [c] N.D. = not detected. [d] **2a** (0.22 mmol, 1.1 equiv). [e] 30 °C. [f] 50 °C

As a model reaction, phenylacetylene **1a** was treated with methyl 2-bromobenzoate **2a** in *N*,*N*-dimethylformamide (DMF) under nitrogen atmosphere at 100 °C (Table 1). An extensive screening of the reaction parameters revealed that both the copper catalyst and base were essential ingredients for the reaction. The absence of any of them led to failure of the formation of the desired product (Table 1, entries 1–3). For copper catalysts, CuI showed the highest catalytic efficiency, giving the *6-endo-dig* cyclization product **3a** in a 90% GC yield. When CuCl and CuBr were employed as the catalysts, the cyclization reaction of **1a** with **2a** produced **3a** in 62% and 36% yields, respectively (Table

**Table 2**

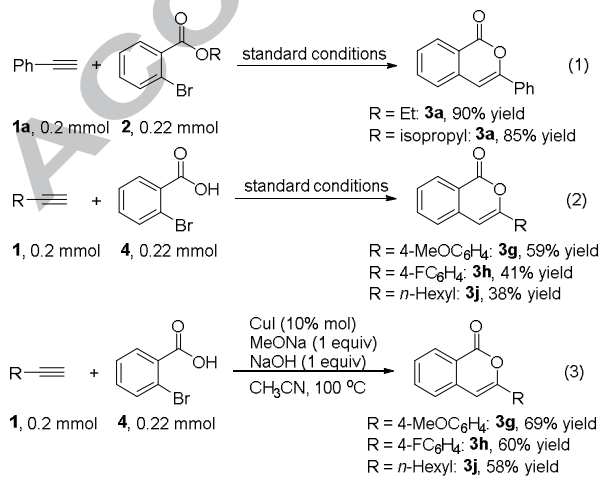
Copper-catalyzed annulation of 2-bromobenzoic esters with terminal alkynes[a]



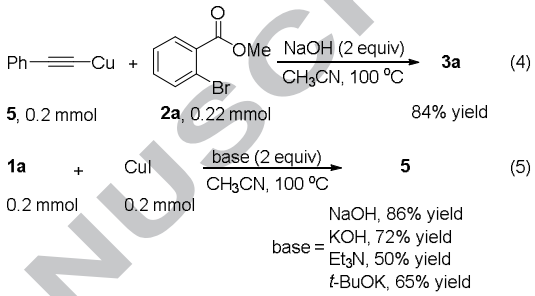

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.22 mmol), CuI (0.02 mmol), NaOH (0.4 mmol), solvent (1.0 mL), $N_2$, 24 h, isolated yields.

1, entries 4 and 5). Whereas CuO, $CuCl_2$, $CuBr_2$, and $Cu(OH)_2$ were inefficient for the reaction (Table 1, entries 6–9). The common inorganic base NaOH played the pivotal role in this reaction probably due to its suitable basicity that favored the formation of copper(I) acetylide intermediate (*vide infra*). In contrast, $Et_3N$, $Na_2CO_3$, $K_2CO_3$ and $Cs_2CO_3$ were inefficient for the reaction, and the strong bases such as *t*-BuONa, *t*-BuOK and KOH gave low yields of the corresponding product (Table 1, entries 10–16). The reaction could be slightly improved by replacement of DMF with $CH_3CN$, and **3a** was obtained in a 92% yield. Other solvents such as DMSO and dioxane were inferior to DMF (Table 1, entries 17–19). When 1.1 equiv of **2a** was loaded, the yield of **3a** was further increased to 95% (Table 1, entry 20). It was noted that the reaction proceeded with excellent regioselectivity, and the *5-exo-dig* annulation product (phthalide) was not detected at all (see SI for details). In addition, the reaction temperature was lowered down to 30 and 50 ºC, *5-exo-dig* product (phthalide) also was not formed, only trace product **3a** was detected (Table 1, entries 21 and 22).

Next, different terminal alkynes and 2-bromobenzoic esters were surveyed under the optimal reaction conditions. As shown in Table 2, this copper-catalyzed system exhibits a wide substrate scope and functional group tolerance, producing a variety of 3-substituted isocoumarins in good to excellent yields. Aromatic terminal alkynes could react smoothly with 2-bromobenzoic esters to give the corresponding isocoumarins in 70–93% isolated yields. Steric hindrance has a slightly detrimental effect on the reaction (Table 2, **3a–d**), and electronic properties of substituents on the phenyl ring did not show obvious effect on the formation of 3-substituted isocoumarins (**3e–i**). Aliphatic alkynes were also good substrates for the reaction, and the high yields of the corresponding products (79–95%, Table 2, **3j–q**) were obtained regardless of the steric hindrance and electronic effect of the substituents. Notably, when a terminal alkyne and an internal alkyne were present in one molecule, only the terminal alkyne participated in the reaction to furnish an alkynyl functionalized isocoumarin (yield: 76%, Table 2, **3r**). Substituted 2-bromobenzoic esters worked well with various terminal alkynes, furnishing the corresponding products in high yields (75–97%, Table 2, **3s–zf**). Remarkably, when 2,5-dibromobenzoic ester was used as substrate, the *ortho*-bromo atom was selectively activated, and the corresponding products were generated in 65% and 71% yields, respectively (Table 2, **3x** and **3zd**), remaining the 5-bromo atom untouched. This survival of bromide offered an opportunity for further functionalization to provide more valuable isocoumarin derivatives.[5a,17]



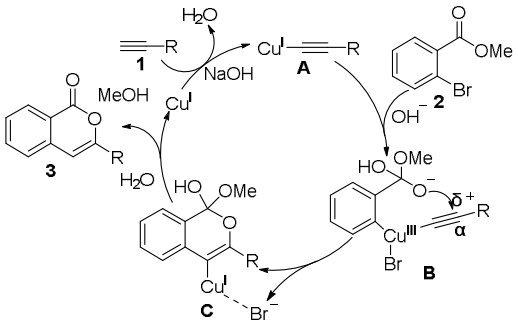

The generality of this cyclization reaction was further demonstrated by using other 2-bromobenzoates as substrates, exemplified by ethyl 2-bromobenzoate and isopropyl 2-bromobenzoate, yielding the corresponding product **3a** in 90% and 85% yields, respectively (eq 1). When 2-bromobenzoic acid (**4**) was used as substrate, the desired 3-substituted isocoumarins were produced in 38–59% yields, which are much lower than those of 2-bromobenzoic esters (eq 2). To confirm this suggestion, 1eq NaOMe, which might produce 2-bromobenzoate with 2-bromobenzoic acid in situ by equilibrium, was added to the reaction system, the yields of the corresponding products were improved (eq 3). The above results suggested that 2-bromobenzoic esters showed better performances than those of bromobenzoic acids in the annulation reaction and bromobenzoic esters other than bromobenzoic acids were involved in the reaction process.




**Scheme 3.** Control experiments.

To gain insight into the mechanism of the reaction, control experiments were conducted (Scheme 3). At first, The reaction of copper(I) phenylacetylide **5** with **2a** was performed, which gave **3a** in a 84% yield (eq 4). Copper(I) phenylacetylide **5** could be readily formed under the reaction conditions (86% yield, eq 5). These results suggested that copper(I) acetylide served as the reaction intermediate. Other bases, such as KOH, $Et_3N$ and *t*-BuOK, that were inferior to NaOH gave copper(I) phenylacetylide **5** in lower yields (72, 50, and 65%, respectively, eq 5) under similar reaction conditions.

On the basis of the control experiments and related reports,[15,16] a plausible catalytic cycle is proposed as outlined in Scheme 4. Firstly, alkyne **1** reacts with CuI in the presence of NaOH to generate the copper(I) acetylide **A**, and then oxidative addition of **A** with hydroxylated methyl 2-bromobenzoate **2** in the presence of NaOH gives a acetylide **B**. The regioselective nucleophilic attack of the negative oxygen atom on α-position of alkyne together with the subsequent reductive elimination gives a *6-endo-dig* annulation intermediate **C**.[6a,18] Finally, The intermediate **C** is hydrolyzed to the desired compound **3**, with concomitant regeneration of the Cu(I) species.




**Scheme 4.** Proposed mechanism of the copper-catalyzed annulation of 2-bromobenzoic esters with terminal alkynes.

In conclusion, we have successfully developed a simple one-pot synthesis of 3-substituted isocoumarins via copper-catalyzed cyclization of 2-bromobenzoic esters with terminal alkynes. Compared to 2-bromobenzoic acids, 2-bromobenzoic esters are more suitable for the annulation reaction, which show very high efficiency and excellent regioselectivity. The easily accessible substrates, ease of operation, satisfactory yields and excellent regioselectivity make it very practical for the synthesis of the useful 3-substituted isocoumarin derivatives.

## Acknowledgments

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## Supplementary data

Supplementary data including the experimental details, NMR spectra, and analytical data of products **3** may be available free of charge via the Internet or the author. Supplementary data associated with this article can be found in the online version.

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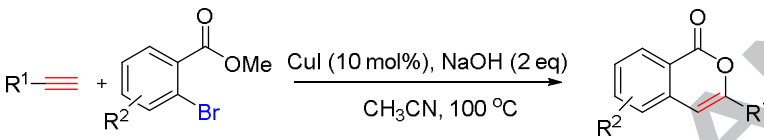
- A highly convenient synthesis for 3-substituted isocoumarins under mild conditions.
- 2-Bromobenzoic esters show high efficiency and excellent regioselectivity.
- An alternative annulation pattern of 2-halobenzoic acids and their derivatives with alkynes is presented.

# Copper-Catalyzed Annulation of 2-Bromobenzoic Esters with Terminal Alkynes towards 3-Substituted Isocoumarins

Mengli Sun, Lebin Su, Jianyu Dong, Long Liu, Yongbo Zhou and Shuang-Feng Yin




$R^1$ = aryl, alkyl

$R^2$ = H, F, Cl, Br, Me, MeO

- mild conditions
- high yield and regioselectivty
- wide functional group tolerance

19.