



Palladium/copper-catalyzed tandem Sonogashira coupling/lactonization of methyl 2-(2',2'-dibromovinyl)benzoate with terminal alkynes: Facile access to 3-alkynyl isocoumarins

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ABSTRACT

An efficient palladium/copper-catalyzed tandem Sonogashira reaction/lactonization of methyl 2-(2',2'-dibromovinyl)benzoate with terminal alkynes has been developed. This facile and direct approach furnishes a variety of 3-alkynyl isocoumarins in moderate to good yields under mild reaction conditions. Furthermore, this method enables concise total synthesis of natural products 3'-hydroxycorfin and gymnopolynes A.

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Isocoumarins, a class of naturally occurring lactones, are not only well known to display a wide range of biological activities, including antibacterial, antifungal, anti-inflammatory, phytotoxic, cytotoxic, and other properties, but also significant synthetic precursors for the assembly of structurally complex target molecules [1]. As important members of isocoumarin family, 3-substituted isocoumarins are key structural features of many natural products (Fig. 1) [2]. In this regard, traditional and recent transition metal-catalyzed synthetic strategies have been developed for the synthesis of 3-substituted isocoumarins [3]. In 2017, a general methodology for the palladium-catalyzed synthesis of 3-substituted isocoumarins from 2-halobenzoates and ketones was realized by Motti and co-workers [3a]. Mohapatra and co-workers presented a gold(I)-catalyzed cyclization for the synthesis of 8-hydroxy-3-substituted isocoumarins [3b]. Later, Jiang and Wu described an efficient and robust protocol for the construction of 3-substituted isocoumarins via palladium-catalyzed nucleophilic addition/oxidative annulation of bromoalkynes with benzoic acids [3c]. However, these transformations are only applicable to the synthesis of 3-arylated and alkylated isocoumarins. There are only limited reports for the preparation of 3-alkynyl isocoumarins (Scheme 1) [4]. Noticeably, 3-alkynyl isocoumarins are not only present in some natural products [5], but also could serve as ideal building blocks

for elaboration of more complex molecular structures owing to versatile applications of the C–C triple bond [6]. Therefore, a straightforward method allowing for facile access to these attractive compounds is still highly desirable.

Over the past two decades, *gem*-dihaloolefins have become valuable building blocks in a variety of transition metal-catalyzed chemical transformations due to versatile reactivity of the vinyl dihalide functionality [7]. Of particular interest is the increasing area of heterocyclic synthesis using *gem*-dihaloolefins as the reaction partners through tandem processes initiated by various metal catalysts, and many impressive transformations have been established [7,8]. In conjunction with our interest in the chemistry of vinyl dibromides [9], we have disclosed a straightforward and efficient method for the synthesis of 3-alkyl isocoumarins via the PdCl₂/CuI-catalyzed tandem formation of C–C and C–O bonds between 2-(2',2'-dibromovinyl)benzoate and terminal alkynes, and herein we report these results.

Our initial investigations commenced with the reaction of 2-(2',2'-dibromovinyl)benzoate **1** and terminal alkyne **2a** in the presence of 10 mol% of CuI, 40 mol% of PPh₃, 10 mol% of PdCl₂, and 2.5 equiv of Cs₂CO₃ in THF at 70 °C under an argon atmosphere for 11 h. The model reaction gave an encouraging 40% isolated yield of desired product **3a** (Table 1, entry 1). Solvent screening revealed that the reaction was sensitive to solvent and a mixed solvent consisting of THF and *i*-PrOH was found to be much better than other solvents (Table 1, entries 1–5). The catalytic efficiency

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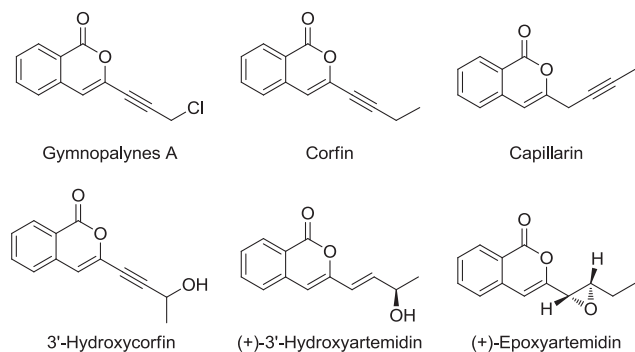


Fig. 1. Representatives of naturally occurring 3-substituted isocoumarins.

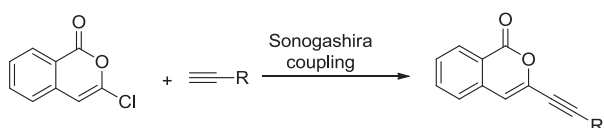
to other bases, such as TEA, DIPEA, K_2CO_3 , and Na_2CO_3 , failed to improve the product yield (Table 1, entries 14–17).

With the optimized conditions in hand, the scope and limitations of this reaction with respect to terminal alkynes **2** were surveyed. As shown in Table 2, a variety of terminal alkynes was smoothly transformed under the standard conditions to provide the desired 3-alkynyl isocoumarins **3b–q** in moderate to good yields. Among them, reactions of 2-(2',2'-dibromovinyl)benzoate **1** with aliphatic alkynes, such as pent-1-yne **2b**, hex-1-yne **2c**, 4-methylpen-1-yne **2d**, and 3,3-dimethylbut-1-yne **2e**, afforded corfin analogues **3b–e** in 57–75% yields. Likewise, other *O*-*t*-butyldimethylsilyl substituted alkynols were also applicable substrates in this reaction, leading to the corresponding 3-substituted isocoumarins **3i–m** in moderate yields. Notably, unprotected alkynols like but-3-yn-2-ol **2n** and prop-2-yn-1-ol **2o** could react with **1** smoothly to furnish 3'-hydroxycorfin [2] **3n** in 59% yield and precursor **3o** of gymnopalyne A in 61% yield, respectively. Despite the steric hindrance of the substituents, both trimethylsilylacetylene **2p** and triethylsilylacetylene **2q** were also proven to be effective substrates to give the corresponding products **3p–q**, which could undergo a deprotective process to form 3-ethynyl isocoumarin.

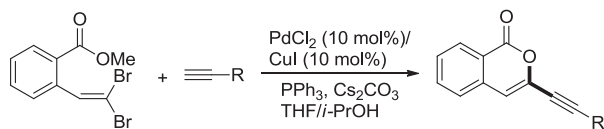
To demonstrate the synthetic value of this methodology, we employed it as a key step to synthesize natural product gymnopalyne A **4**. Gymnopalyne A, a chlorinated isocoumarin, was isolated from cultures of the basidiomycete *Gymnopus sp.* by Stadler and co-workers in 2013, and exhibited weak to moderate antimicrobial and pronounced cytotoxic activities [2]. As depicted in Scheme 2, the molecule could be easily obtained by the treatment of **3o** with PPh_3 in CCl_4 under reflux.

On the basis of previous reports [10], a plausible reaction mechanism is proposed in Scheme 3. First, oxidative addition of Pd(0) species to the (*E*)-bromide of 2-(2',2'-dibromovinyl)benzoate **1** occurs to produce Pd(II) intermediate **A**, which then undergoes transmetalation with the copper(I)-acetylide **B** followed by reductive elimination to afford the monobromovinyl intermediate **D** with concomitant regeneration of the Pd(0) species. Second, the

Previous work:



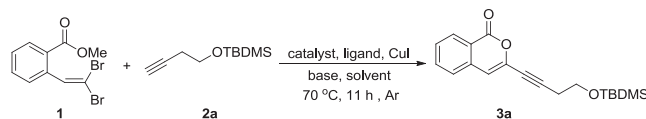
This work:



Scheme 1. Approaches to 3-alkynyl isocoumarins.

of different palladium catalysts, including $PdCl_2(PPh_3)_2$, $Pd_2(dba)_3$, $Pd(PPh_3)_4$, $[PdCl(C_3H_5)]_2$, and $Pd(OAc)_2$, was then tested. $PdCl_2$ was proven to be the best choice for the reaction, and yielded **3a** in 69% yield (Table 1, entries 5–10). Next, different phosphine ligands were screened, but they were found to be inferior to PPh_3 under the given conditions (Table 1, entries 11–13). Switching the Cs_2CO_3

Table 1
Optimization of the reaction conditions.^a



Entry	Pd source	Ligand	Base	Solvent	Yield (%) ^b
1	$PdCl_2$	PPh_3	Cs_2CO_3	THF	40
2	$PdCl_2$	PPh_3	Cs_2CO_3	Toluene	34
3	$PdCl_2$	PPh_3	Cs_2CO_3	DMF	37
4	$PdCl_2$	PPh_3	Cs_2CO_3	MeCN	32
5	$PdCl_2$	PPh_3	Cs_2CO_3	THF/ <i>i</i> -PrOH	69
6	$PdCl_2(PPh_3)_2$	PPh_3	Cs_2CO_3	THF/ <i>i</i> -PrOH	32
7	$Pd_2(dba)_3$	PPh_3	Cs_2CO_3	THF/ <i>i</i> -PrOH	35
8	$Pd(PPh_3)_4$	PPh_3	Cs_2CO_3	THF/ <i>i</i> -PrOH	47
9	$[PdCl(C_3H_5)]_2$	PPh_3	Cs_2CO_3	THF/ <i>i</i> -PrOH	39
10	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	THF/ <i>i</i> -PrOH	44
11	$PdCl_2$	Ad_2PBU	Cs_2CO_3	THF/ <i>i</i> -PrOH	26
12	$PdCl_2$	PCy_3	Cs_2CO_3	THF/ <i>i</i> -PrOH	43
13	$PdCl_2$	TFP	Cs_2CO_3	THF/ <i>i</i> -PrOH	58
14	$PdCl_2$	PPh_3	TEA	THF/ <i>i</i> -PrOH	25
15	$PdCl_2$	PPh_3	DIPEA	THF/ <i>i</i> -PrOH	39
16	$PdCl_2$	PPh_3	K_2CO_3	THF/ <i>i</i> -PrOH	26
17	$PdCl_2$	PPh_3	Na_2CO_3	THF/ <i>i</i> -PrOH	24

^a Reaction conditions: **1** (0.63 mmol), **2a** (1.5 equiv), Pd source (10 mol%), ligand (40 mol%), CuI (10 mol%), base (2.5 equiv), solvent (10 mL, if *i*-PrOH was added, the ratio is 9:1), argon atmosphere, 70 °C, 11 h.

^b Isolated yield.

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