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Synthesis of 4-Arylcoumarins via Cu-Catalyzed Hydroarylation with Arylboronic Acids

Yoshihiko Yamamoto* and Naohiro Kirai

Department of Applied Chemistry, Graduate School of Science and Engineering, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152-8552, Japan

omyy@apc.titech.ac.jp

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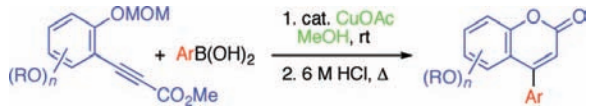
ABSTRACT



In the presence of 2−4 mol % of CuOAc, methyl phenylpropiolates having a MOM-protected hydroxy group at the ortho position underwent hydroarylation with various arylboronic acids in MeOH at ambient temperature, resulting in the formation of 4-arylcoumarins in high yields after the acidic workup. This method was effectively used for the synthesis of biologically active natural and artificial compounds.

Coumarin (2*H*-1-benzopyran-2-one) is a privileged oxygen heterocycle widely distributed throughout the plant kingdom.[1] Among naturally occurring coumarins, 4-aryl derivatives (neoflavones), which constitute a subgroup of flavonoids, have received considerable attention since they exhibit important biological activities[2] such as anti-HIV,[3] antimalarial,[4] antibacterial,[5] and cytotoxic.[6] In addition, several natural and synthetic polyoxygenated 4-arylcoumarins have been evaluated as the nonisomerizable analogues of combretastatin A-4, which is an important antitubulin agent that interacts with the binding site of colchicine.[7] Conventionally, 4-arylcoumarins have been obtained from phenols by means of condensation reactions with carbonyl compounds such as Pechmann or Perkin reactions,[8] while they are also synthesized currently through catalytic hydroarylations with propiolates.[9] However, devising new synthetic routes that yield various types of derivatives in a divergent manner would be highly useful in terms of discovery of new drugs.[10] In this respect, the transition-metal-catalyzed coupling reactions are highly promising tools since they effectively introduce various arene rings into the coumarin framework at a later

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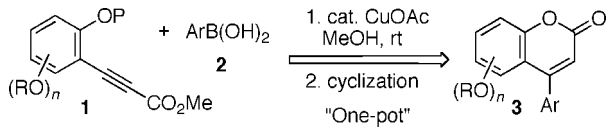
stage of the synthetic sequence. Palladium-, rhodium-, or nickel-catalyzed cross couplings of coumarin scaffolds with a coupling point at the 4 position have been developed by several research groups.[11] Cacchi and co-workers have recently devised the domino Heck coupling/cyclization method.[12] This method is useful since readily available cinnamates and aryl halides can be coupled together to form 4-arylcoumarins directly.

We have previously reported that the *syn* hydroarylation of propiolates with arylboronic acids proceeds even at ambient temperature without additives upon treatment with an inexpensive copper catalyst in methanol.[13] As a continuation of this study, we herein synthesize 4-arylcoumarins **3** via the Cu-catalyzed hydroarylation of phenol-derived propiolates **1** with arylboronic acids **2** and subsequent cyclization (Scheme 1).

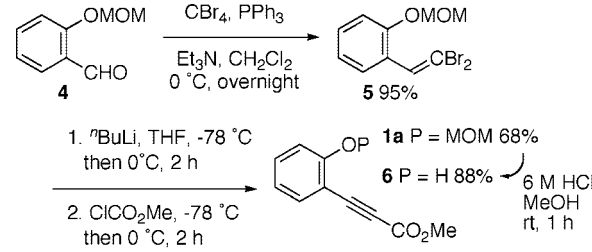
Scheme 1



The catalytic hydroarylation of alkynes and their subsequent cyclization have been employed thus far for the syntheses of butenolides,[14] chromenes,[15] and quinolines;[16] however, no example of the direct synthesis of 4-arylcoumarins along this line has been reported as far as we know.

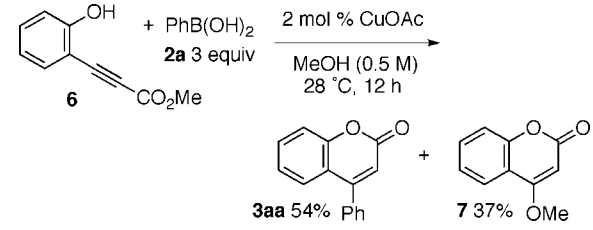
Our study commenced with the preparation of phenol-derived propiolate substrates (Scheme 2). Cacchi et al. reported that the Sonogashira coupling of *o*-iodophenol with ethyl propiolate gave protection-free *o*-alkynylphenol **6** in 30% yield, while a similar coupling of the THP-protected analogue led to a mixture of **6** and its THP ether (P = THP).[15c] Hence, we examined the alternative route reported by Sato and co-workers.[17] Readily available MOM-protected salicylaldehyde **4** was treated with CBr_4 (1.3 equiv), PPh_3 (2.6 equiv), and Et_3N (1 equiv) in CH_2Cl_2 at 0 °C overnight to obtain dibromoalkene **5** in 95% yield. The isolated **5** was then converted into propiolate **1a** in 68% yield upon treatment with ^{n}BuLi (2.2 equiv) in THF and subsequently with $ClCO_2Me$ (1.5 equiv). Finally, deprotection under acidic conditions uneventfully gave **6** in 88% yield.

Scheme 2



Having secured a reliable route to the alkyne substrates, we then attempted the synthesis of 4-arylcoumarins via Cu-catalyzed hydroarylation/cyclization. In our previous report, we described that the Cu-catalyzed hydroarylation of methyl 4-hydroxy-2-butynoate with phenylboronic acid gave 3-phenylbutenolide in 61% yield.[13] Similarly, **6** was first subjected to hydroarylation conditions (Scheme 3). As a result,

Scheme 3



4-phenylcoumarin **3aa** was obtained in 54% yield; however, unexpectedly, 4-methoxycoumarin **7** was also formed in 37% yield. Although the details are unclear, it is reasonable to assume that the *o*-hydroxy group played some role in facilitating the addition of methanol because no such methoxylation product was observed in the corresponding *o*-methoxyphenylpropiolate in our previous study.[13] In this

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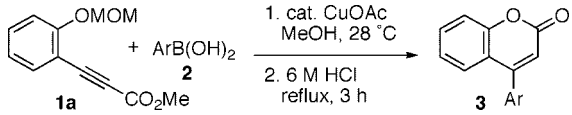
respect, the MOM-protected **1a** was a promising substrate as the MOM protection probably suppressed the methoxylation and was readily removed after hydroarylation. In fact, **1a** underwent smooth hydroarylation within 6 h under the same conditions, and upon treatment with 6 M HCl in refluxing MeOH in the same pot, the desired coumarin **3aa** was formed in 89% yield as an exclusive product (Table 1, entry 1).

Table 1. Cu-Catalyzed Hydroarylation/Cyclization of **1a**[a]



entry	**2**, Ar	Cu (mol %)	time (h)	**3**, yield (%)
1	**2a**, C_6H_5	2	6	**3aa**, 89
2	**2b**, *p*-MeC_6H_4	2	6	**3ab**, 90
3	**2c**, *m*-MeC_6H_4	2	6	**3ac**, 93
4	**2d**, *o*-MeC_6H_4	4	6	**3ad**, 89
5	**2e**, *p*-$MeOC_6H_4$	2	2	**3ae**, 90
6	**2f**, *p*-ClC_6H_4	4	6	**3af**, 88
7	**2g**, *p*-IC_6H_4	4	6	**3ag**, 89
8	**2h**, *p*-$OHCC_6H_4$	4	3	**3ah**, 89
9	**2i**, *m*-$O_2NC_6H_4$	10	6	**3ai**, 87
10	**2j**, 2-naphthyl	2	6	**3aj**, 75

[a] **1a** (0.5 mmol), **2** (3 equiv), MeOH (1 mL, 0.5 M); 6 M HCl (4 mL)/MeOH (4 mL).

We further checked the scope of this method in terms of arylboronic acids as summarized in Table 1. All tolylboronic acids **2b**−**d** having a methyl group at the *para*, *meta*, or *ortho* positions, respectively, gave the desired coumarins **3ab**−**ad** in high yields, although higher catalyst loading was required for **2d** (entries 2−4). Neither electron-donating nor electron-withdrawing groups gave a deleterious effect on the formation of coumarins **3ae** and **3af**−**ai** (entries 5 and 6−9). More importantly, this protocol could be applied to arylboronic acids having a labile functional group, such as **2g** and **2h**, efficiently affording the corresponding coumarins **3ag** and **3ah** without the loss of the reactive C−I bond or the formyl group (entries 7 and 8). These functional groups are useful synthetic handles for further derivatizations (vide infra).

To demonstrate the synthetic utility of our method, we have applied the method to the synthesis of natural products. The plants belonging to the Dalbergia family have been known to possess unique medicinal properties. Naturally, the identification of their constituents relevant to the biological activities is highly important. Thus far, various 4-arylcoumarins have been isolated, and their structures have been characterized by their phenyl rings multiply oxygenated in several substitution patterns.[1c] Their synthesis is hence an attractive testing ground for our flexible method: the combinations of only three arylpropiolates **1b**−**d** with readily available arylboronic acids **2a**,**k**−**m** would cover the synthesis of seven natural products (Figure 1 and Table 2).

First, alkynoate **1b** was coupled with known 3-(*tert*-butyldimethylsilyloxy)-4-methoxyphenylboronic acid **2k**[18]

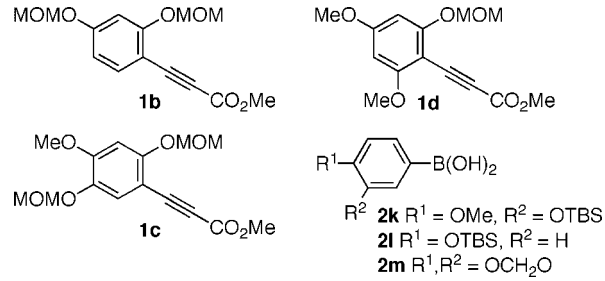


Figure 1. Coupling components for the synthesis of natural 4-arylcoumarins.

under standard conditions to obtain volubolin **3bk** in 93% yield (Table 2, entry 1).[19] Next, dalbergin **3ca**, which is the oldest known and most common 4-arylcoumarin constituent,[20] was obtained in 92% yield from alkynoate **1c** and phenylboronic acid **2a** (entry 2). Similarly from **1c**, melanneine[21] **3ck** and melanettin[22] **3cl** were synthesized in high yields using the TBS-protected phenolic boron reagents **2k** and **2l**, respectively (entries 3 and 4). Other types of natural neoflavones isolated from *Coutarea hexandra* were also synthesized from alkynoate **1d**.[23] The combination of **1d** with arylboronic acids **2k**−**m** gave **3dk**−**3dm**, respectively, in good yields although increased catalyst loadings of 4 mol % were required under the steric effect of the 5-methoxy group (entries 5−7). The formation of **3dk**, which has also been isolated from other plant origins, is of particular importance since it has been reported to exhibit interesting biological activities such as cytotoxic activities against human tumor cell lines,[24] antiplasmodial activity against *Plasmodium falciparum*,[4a] and inhibition of microtubule assembly without influencing human topoisomerases I and II.[7]

Further illustrations of the synthetic utility are outlined in Scheme 4. Tunge et al. have reported the elegant one-pot tandem Pd(II)-catalyzed cyclization/Pd(0)-catalyzed cross coupling process that efficiently provides highly substituted 4-arylcoumarins.[25] With the 4-arylcoumarin products **3ag** and

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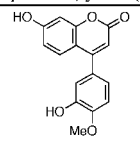
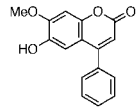
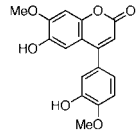
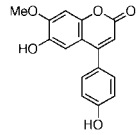
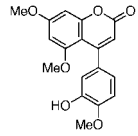
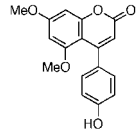
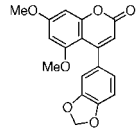
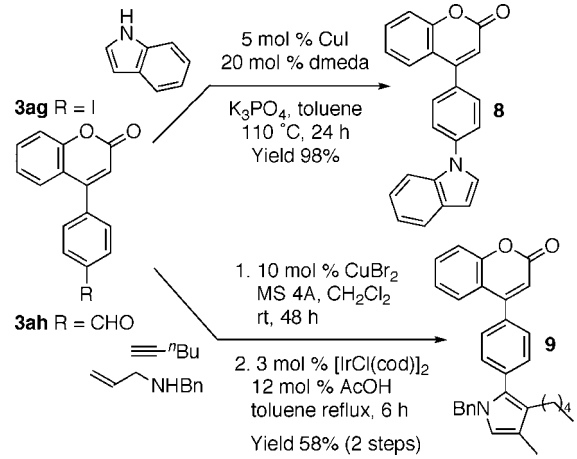
Table 2. Synthesis of Coumarins from Arylalkynoates **1b**−**c**[a]

entry	substrates	Cu (mol %)	product, yield (%)
1	**1b** / **2k**	2	 **3bk**, 93
2	**1c** / **2a**	2	 **3ca**, 92
3	**1c** / **2k**	2	 **3ck**, 98
4	**1c** / **2l**	2	 **3cl**, 94
5	**1d** / **2k**	4	 **3dk**, 76
6	**1d** / **2l**	4	 **3dl**, 76
7	**1d** / **2m**	4	 **3dm**, 78

[a] **1** (0.5 mmol), **2** (3 equiv), MeOH (1 mL, 0.5 M), 28 °C, 6 h; 6 M HCl (4 mL)/MeOH (4 mL), reflux, 3 h.

3ah having the C−I bond or the formyl group on the 4-phenyl ring in hand, we have attempted to realize sequential processes that provide nitrogen heterocycles. First, **3ag** was subjected to Ullmann coupling with indole using the Cu(I)/*N*,*N*′-dimethylethylenediamine (dmeda) catalyst system developed by Buchwald et al.[26] to obtain **8** in 98% yield. We then applied our own sequential Cu-catalyzed Mannich reaction/Ir-catalyzed cycloisomerization process.[27] Gratifyingly, we could obtain the pyrrole-substituted product **9** in 58% yield from **3ah**, *N*-benzylallylamine, and 1-hexyne.

Scheme 4



In conclusion, we have established an efficient Cu-catalyzed coupling to synthesize 4-arylcoumarins. This protocol is compatible with phenylboronic acids having various functional groups including carbon-halogen bonds as well as an aldehyde. By applying this protocol, we have synthesized seven naturally occurring neoflavones in good yields. Further, the present Cu-catalyzed hydroarylation/cyclization was combined with Cu-catalyzed Ullmann coupling or Cu-catalyzed Mannich reaction/Ir-catalyzed cycloisomerization to produce N-heterocycle-substituted 4-arylcoumarins with interesting applications.

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Supporting Information Available: Experimental procedures and analytical data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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