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Synthesis of highly substituted isocoumarins by rhodium-catalyzed annulation of readily available benzoic acids

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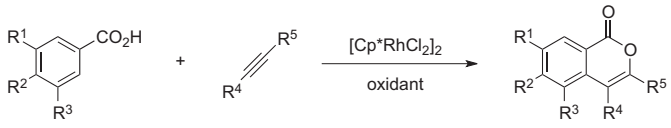
ABSTRACT

Readily available benzoic acids possessing a number of oxygen-containing group(s) efficiently undergo oxidative coupling with alkynes through regioselective C–H bond cleavage under rhodium catalysis to form highly substituted isocoumarin derivatives. Such isocoumarins are of considerable interest due to their unique biological properties.

1. Introduction

Multiply hydroxy- and methoxy-substituted benzoic acids including gallic acid, syringic acid, and vanillic acid are widely present in plants and are readily available from biomass.[1] Especially, they become more promising as building blocks, along with the development of their production from abundant lignin. However, the derivatization methods of such sustainable starting materials have been less explored and thus their development is strongly desired. Although few basic reactions, such as decarboxylation,[2] esterification,[3] and amidation[4] have been performed, to our knowledge, there is no report for their direct coupling involving C–C bond formation, nor application to heterocycle synthesis.

On the other hand, we have continuously studied on developing new coupling methods of aromatic carboxylic acids with unsaturated compounds under transition-metal catalysis.[5] Recently we reported the rhodium-catalyzed oxidative coupling of simple benzoic acid with internal alkynes[5j,k] involving C–H bond cleavage[6] to produce isocoumarin derivatives. In the context of our work, it has been revealed that this annulation procedure is applicable to polysubstituted benzoic acids possessing a number of oxygen-containing substituents, which are readily preparable from gallic, syringic, and vanillic acids, to form the corresponding highly substituted isocoumarin derivatives (Scheme 1). Such isocoumarins have been of considerable interest due to their unique biological properties.[7] Compared with conventional multi-step synthetic methods, the present direct annulation process is dramatically more atom- and step-economical. The results obtained for the annulation are described herein.



1a-e 2a-i 3a-i,5-8

Scheme 1. Annulation of substituted benzoic acids **1**.

2. Results/discussion

In an initial attempt, the reaction of 3,4,5-trimethoxybenzoic acid (**1a**) with diphenylacetylene (**2a**) was examined under conditions similar to those previously employed for the reaction of unsubstituted benzoic acid with **2a**,[5j,k] using $[Cp^*RhCl_2]_2$ ($Cp^*=\eta^5$-pentamethylcyclopentadienyl; 1 mol %) and $Cu(OAc)_2\cdot H_2O$ (2 equiv) as catalyst and oxidant, respectively, in *o*-xylene at 120 °C under N_2 (conditions A). As a result, their oxidative coupling product, 5,6,7-trimethoxy-3,4-diphenylisocoumarin (**3a**), was obtained in 64% yield ($R^1=R^2=R^3=OMe$, $R^4=R^5=Ph$ in Scheme 1; entry 1 in Table 1).

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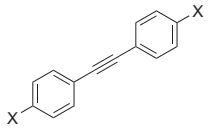
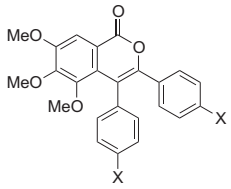
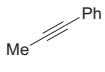
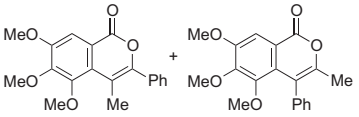
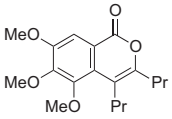
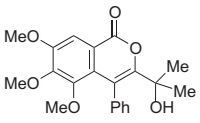
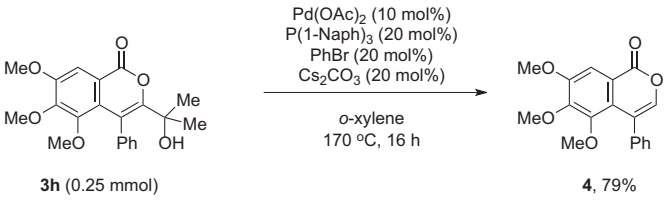
Throughout the whole study the choices of solvent and oxidant were found to be important, depending on the solubilities and reactivities of substrates. In this case, the use of DMF as solvent (conditions B) brought about the improvement of the yield of **3a** up to 86% yield (entry 2). Under conditions B, methyl-, methoxy-, chloro-, and trifluoromethyl substituted diphenylacetylenes **2b**–**e** also reacted with **1a** smoothly to produce the corresponding isocoumarins **3b**–**e** (entries 2–6). The reaction of **1a** with 1-phenyl-1-propyne (**2f**) proceeded efficiently to afford isolable isocoumarin **3f** predominantly, along with a minor amount of **3f′** (entry 7). The coupling with 4-octyne (**2g**) was sluggish under conditions B (entry 8). It was found that the reaction efficiency was improved by using Ag_2CO_3 as oxidant in place of $Cu(OAc)_2\cdot H_2O$ in *o*-xylene (entry 9). Treatment of **1a** with 2-methyl-4-phenyl-3-butyn-2-ol (**2h**) did not give any annulation product at all under the standard conditions B (entry 10). In this case using $Cu(OAc)_2\cdot H_2O$, alkyne dimerization took place prior to coupling with **1a** to form 1,4-diphenyl-1,3-butadiyne (20%). Fortunately, the use of Ag_2CO_3 suppressed the dimerization and effectively induced the expected reaction. Thus, under the modified conditions, isocoumarin **3h** was produced in 95% yield (entry 11). It should be noted that **3h** was obtained in completely pure form: no regioisomers being detected. The 2-hydroxyprop-2-yl substituent in **3h** was found to be removable upon treatment with a palladium catalyst system, previously developed by us (Scheme 2).[8]

Table 1
Reaction of acid **1a** with alkynes **2**[a]

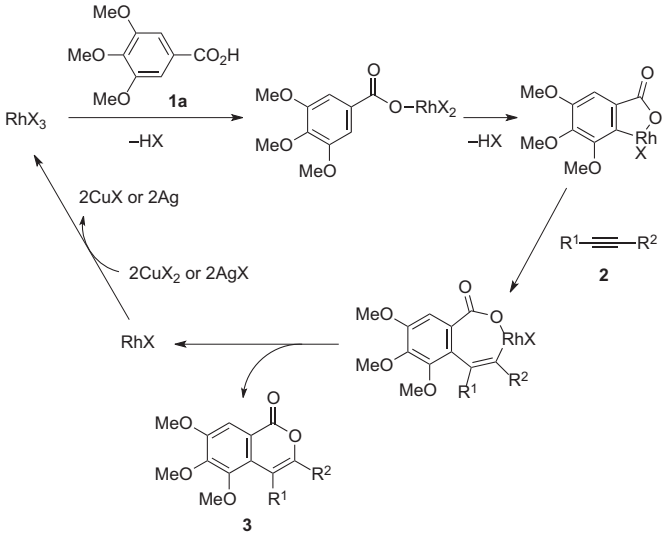
Entry	2	Time (h)	Product(s), % yield[b]
			
1[c]	**2a**: X=H	5	**3a**: X=H, 64 (46)
2	**2a**: X=H	4	**3a**: X=H, (86)
3	**2b**: X=Me	7	**3b**: X=Me, 83 (81)
4	**2c**: X=OMe	6	**3c**: X=OMe, (98)
5	**2d**: X=Cl	5	**3d**: X=Cl, 88 (65)
6	**2e**: X=CF_3	6	**3e**: X=CF_3, (79)
			
7	**2f**	5	**3f**+**3f′**, 85 (76) [4:1]
			
8	**2g**	18	**3g**, 30
9[c,d]	**2g**	5	**3g**, 52 (46)
			
10	**2h**: R=CMe_2(OH)	6	**3h**, 0
11[d]	**2h**: R=CMe_2(OH)	9	**3h**, (95)

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.6 mmol), $[Cp^*RhCl_2]_2$ (0.005 mmol), $Cu(OAc)_2\cdot H_2O$ (1 mmol) in DMF (2.5 mL) at 120 °C for 4–7 h under N_2.
[b] GC yield based on the amount of **1a** used. Value in parentheses indicates yield after purification.
[c] In *o*-xylene (2.5 mL).
[d] Ag_2CO_3 (0.5 mmol) was used in place of $Cu(OAc)_2\cdot H_2O$.



Scheme 2. De(hydroxy)propylation of **3h**.

As was proposed for the oxidative coupling of unsubstituted benzoic acid with alkynes,[5j,k] the present reaction of **1a** seems to proceed through cyclorhodation at the *ortho*-position of a rhodium(III) benzoate intermediate, alkyne insertion to form a seven-membered rhodacycle, and subsequent reductive elimination to produce isocoumarin **3** (Scheme 3). The resulting Rh(I) species may be reoxidized in the presence of a Cu(II) or Ag(I) salt to regenerate a Rh(III) species. In the case using **2h**, **3h** was formed exclusively in a good yield (entry 11 in Table 1). The observed high regioselectivity in the alkyne insertion step may be due to the interaction between hydroxy oxygen in **2h** and the rhodium center.



Scheme 3. A plausible mechanism for the reaction of **1a** with **2**.

The reactions of variously substituted benzoic acids with **2a** were next examined. 4-Acetoxy-3,5-dimethoxybenzoic acid (**1b**) coupled with **2a** under conditions B to produce isocoumarin **5** in a low yield (entry 1 in Table 2). In *o*-xylene, the yield of **5** somewhat increased to 40% (entry 2). Finally, the use of Ag_2CO_3 as oxidant was found to be a key to improve the reaction efficiency. Thus, **5** was obtained in 82% yield (entry 3). Methoxymethyl protected syringic acid **1c** could also be employed for the annulation to form **6**, along with a minor amount of deprotected isocoumarin **6′** (entry 4). Treatment of syringic acid itself with **2a** using Cu or Ag salt oxidant did not give any annulated product at all. Therefore, **6′** appears to be formed via annulation/deprotection. Under similar conditions using Ag_2CO_3 as oxidant in DMF, the reaction of 4-acetoxy-3-methoxybenzoic acid (**1d**) proceeded smoothly to produce isocoumarin **7**, accompanied by formation of a negligible amount of **7′**, arised from annulation at the sterically hindered *ortho*-position (**7**:**7′**=24:1) (entry 5). 3,4-Dimethoxy- (**1e**) and 4-methoxybenzoic acid (**1f**) underwent the coupling even under standard conditions B to smoothly form the corresponding isocoumarins **8**(+**8′**) and **9**, respectively (entries 6 and 7).