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Synthesis of Isocoumarins via Pd/C-Mediated Reactions of *o*-Iodobenzoic Acid with Terminal Alkynes†

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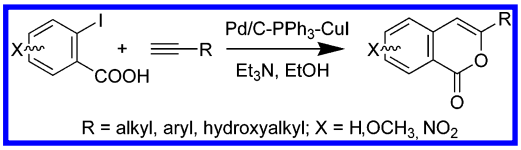

The coupling reaction of *o*-iodobenzoic acid with terminal alkynes by using a catalyst system of 10% Pd/C−Et_3N−CuI−PPh_3 has been studied in a variety of solvents. 3-Substituted isocoumarins were formed in good yields and with good regioselectivity when the reaction was performed in EtOH.

Introduction

The prevalence of isocoumarins[1] in numerous natural products that exhibit a wide range of pharmacological activities, such as antifungal,[2] antimicrobial,[3] phytotoxic,[4] and other effects, has led to a continued interest in the practical synthesis of this class of lactones, especially 3-substituted isocoumarins. Considerable efforts have been directed toward the synthesis of isocoumarins,[5] via either traditional or transition-metal-catalyzed reactions. Among these, the Sonogashira type coupling followed by the electrophilic[6] or transition-metal-mediated cyclization of the resulting alkynes possessing a carboxylate or an equivalent group in proximity to the triple bond has emerged as the most important process for the construction of the isocoumarin ring (Figure 1). Thus, isocoumarins have been prepared via cyclization of 2-(1-alkynyl)benzoic acids/esters or amides in the presence of a number of reagents: e.g., mineral acid[5e] or HBF_4,[5j] $PdCl_2(CH_3CN)_2$,[1f] and silver,[7a−c] mercury,[7d,e] and copper salts.[8a] Cyclization of *o*-phenylethynylbenzonitrile in the presence of $HgSO_4$[7d] or $Ru_3(CO)_{12}$[8b] leading to the 3-phenylisocoumarin has also been reported. In an earlier effort directed toward the one-pot synthesis of isocoumarins,[5b] the reaction of *o*-iodobenzoic acids with copper acetylides and terminal alkynes was investigated[9] and found to yield phthalides in most of the cases.[9b,c] The use of $PdCl_2$-

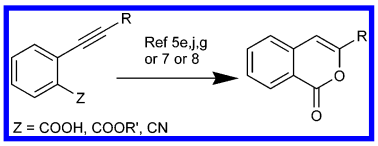

FIGURE 1. Construction of the isocoumarin ring.

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$(PPh_3)_2$–Et_3N–CuI as a catalyst system also exhibited greater selectivity for phthalides for a variety of terminal acetylenes.[10] However, in a subsequent study Cheng and Liao have shown that isocoumarins could be obtained as major products when *o*-iodobenzoic acid was reacted with terminal alkynes in the presence of $Pd(PPh_3)_4$, Et_3N, and a stoichiometric amount of $ZnCl_2$.[11] The use of $ZnCl_2$ in place of CuI was found to be responsible for the predominant formation of isocoumarins over phthalides. In contrast, we have noted that *o*-iodobenzoic acid reacts smoothly with terminal alkynes in the presence of CuI and Pd/C–Et_3N–PPh_3 as a catalyst system in ethanol, affording the corresponding isocoumarins in good yields. While there have been numerous studies on Pd/C-mediated coupling of aryl halides with terminal acetylenes,[12] to the best of our knowledge the use of Pd/C for the synthesis of isocoumarins or phthalides has never been reported thus far. In this study, we first report the palladium (on charcoal)–copper-mediated synthesis of diversified 3-substituted isocoumarins from *o*-iodobenzoic acid and terminal alkynes.

Results and Discussion

In pursuance of our research under the new drug development program,[13a,b] we became interested in the synthesis of oxygen-containing heterocycles,[13a,c–f] especially 3-substituted isocoumarin, of potential pharmacological interest. Our interest in the 3-substituted isocoumarin originated from the fact that the angiogenesis inhibitor NM-3 (2-(8-hydroxy-6-methoxy-1-oxo-1*H*-2-benzopyran-3-yl)propionic acid),[13g] which belongs to this class, is presently undergoing Phase 1 clinical trials. During our Pd/C-mediated synthesis[14] of 2-substituted benzo[*b*]furans[14a] and indoles[14b] (Figure 2), we were intrigued with the possibility of using Pd/C as a cheap and alternative source of palladium catalyst for the coupling of 2- halobenzoic acid (**I**) with terminal alkynes. Accordingly, we carried out a number of experiments using 10% Pd/C–Et_3N–CuI–PPh_3 as a catalyst system in a variety of solvents (Table 1). At the beginning of our study the reaction was carried out in DMF (entry 1, Table 1) where phthalide (**IIIa**) was isolated as the major product, although in low yield. Notably, DMF was the solvent of choice in the earlier synthesis of phthalides and isocoumarins in the presence of palladium complexes.[15] Switching over from DMF to EtOH, we observed a dramatic change in the product distribution, and the corresponding isocoumarin (**IVa**) was isolated as the sole product in this case (entry 2, Table 1). This observation prompted us to examine the use of other alcohols: e.g., ^{i}PrOH and ^{t}BuOH (entries 3 and 4, Table 1). While the overall yields of products were improved marginally, a considerable amount of phthalide was detected as a side

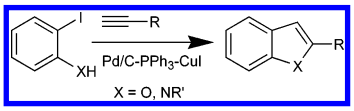
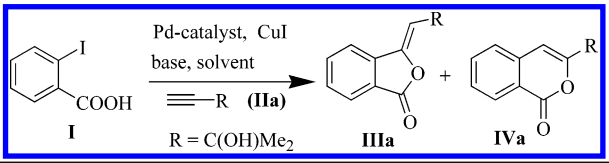


FIGURE 2. Pd/C-mediated synthesis of 2-substituted benzo[*b*]furans and indoles.[14]

TABLE 1. Effect of Reaction Conditions on the Palladium-Catalyzed Coupling Reaction of *o*-Iodobenzoic Acid with 2-Methyl-3-butyn-2-ol[a]



entry	Pd catalyst	base; solvent	yield (%)[b] (**IIIa**:**IVa**)[c]
1	10% Pd/C–PPh_3	Et_3N; DMF	25 (4:1)
2	10% Pd/C–PPh_3	Et_3N; EtOH	75 (**IVa** only)
3	10% Pd/C–PPh_3	Et_3N; ^{i}PrOH	92 (1:4)
4	10% Pd/C–PPh_3	Et_3N, ^{t}BuOH	80 (1:4)
5	10% Pd/C–PPh_3	Et_3N; 1,4-dioxane	85 (9:1)
6	$Pd(PPh_3)_2Cl_2$	Et_3N; EtOH	82 (9:1)
7	$Pd(PPh_3)_4$	Et_3N; EtOH	90 (1:9)
8[d]	10% Pd/C–PPh_3	Et_3N; EtOH	55 (**IVa** only)

[a] Reaction conditions: **I** (1.0 equiv), **IIa** (2.0 equiv), 10% Pd/C or other Pd catalyst (0.03 equiv), PPh_3 (0.12 equiv), CuI (0.06 equiv), Et_3N (5 equiv) in a solvent at 80 °C for 16 h under N_2. [b] Isolated overall yield of **IIIa** + **IVa**. [c] The ratio was determined by ^{1}H NMR analysis. [d] The reaction was carried out for 24 h.

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(15) As noted by Villemin and Goussu initially, in Et_3N alone the reaction mixture containing *o*-iodobenzoic acid became heterogeneous and no reaction was observed. A homogeneous mixture was obtained with dichloromethane, but no reaction took place.[5e] This problem was overcome by Kundu and Pal by using DMF as a cosolvent, where the reaction proceeded smoothly to yield phthalides as major products.[10]

product in such cases. The use of 1,4-dioxane afforded **IIIa** as a major product under the present Pd/C−Cu catalysis (entry 5, Table 1). The use of other catalysts, e.g. $Pd(PPh_3)_2Cl_2$ and $Pd(PPh_3)_4$ (originally used for the synthesis of phthalides and isocoumarins, respectively), were examined (entries 6 and 7, Table 1). Remarkably, $Pd(PPh_3)_4$ showed selectivity for isocoumarin, in contrast to a $Pd(PPh_3)_2Cl_2$-catalyzed reaction where phthalide was isolated as the major product. Nevertheless, unlike the case for Pd/C, the isocoumarin formed in this case was contaminated with the corresponding phthalide (entry 2 vs 7, Table 1). The role of PPh_3 was also evaluated, in the absence of which no desired product was detected under the reaction conditions studied. We then examined the use of LiCl (1−5 equiv) and its effect on the reaction conditions as described above (cf. entry 2, Table 1). The use of LiCl was found to be beneficial for the synthesis of 3,4-disubstituted isocoumarins from 2-iodobenzoate ester and internal alkynes.[5k] Although the reaction was found to be faster (8 h vs 16 h of entry 2, Table 1) when an excess of LiCl (5 equiv) was used in the present synthesis of **IVa**, no significant effect on product ratio (i.e. **IIIa/IVa**) or yield was observed. Thus, after a series of experiments, 10% Pd/C in ethanol proved to be the most effective combination of catalyst and solvent for the synthesis of isocoumarins. This Pd/C-mediated coupling reaction in ethanol was carried out for 16 h, as an increase in reaction time to 24 h or more resulted in the ethanolysis of the product formed under the prolonged heating conditions, thereby decreasing the product yield (entry 8, Table 1).

We were delighted to observe the formation of 3-substituted isocoumarin as a sole product under certain reaction conditions and, therefore, decided to test the reaction conditions with other terminal alkynes. Using the optimized protocol as detailed above (entry 2, Table 1), several 3-substituted isocoumarins were prepared in ethanol. Thus, when *o*-iodobenzoic acid (**I**) was treated with 2 equiv of terminal alkyne (**II**; R = aryl, alkyl, hydroxyalkyl, etc.)[16a] in EtOH in the presence of 10% Pd/C (0.03 equiv), PPh_3 (0.12 equiv), CuI (0.06 equiv), and Et_3N (5 equiv) under a nitrogen atmosphere isocoumarins[16d] (**IV**) were obtained in good yields.

By use of this Pd/C-catalyzed tandem coupling−cyclization process a variety of commercially available terminal acetylenes were reacted with *o*-iodobenzoic acids,[16b,c] and the yields of isolated products (**IV** and **V**) after purifying by column chromatography have been presented in Tables 2 and 3. Various functional groups (including alkyl, hydroxyl, phenyl, etc.) present in acetylenic compounds (**II**) employed so far were well tolerated during the course of the reaction (Table 2). The process was found to be quite general for the preparation of 3-substituted isocoumarins. While a primary or secondary alcohol present in the terminal alkynes was readily accommodated (entries 2−4, Table 2), the presence of a long-chain alkyl group did not affect the coupling−cyclization process (entries 5−7, Table 2). Of particular note, however, are two examples (entries 8 and 9, Table 2) where in one case a significant amount of side product, i.e., 3-phenyl-4-(phenylethynyl)isocoumarin, was isolated along with the desired isocoumarin when phenylacetylene was used (entry 8, Table 2). In another case an alkyne bearing a $SiMe_3$ group afforded the five-membered ring product exclusively after subsequent desilylation of the resulting phthalide in one pot (entry 9, Table 2). 2-((Trimethylsilanyl)ethynyl)benzoic acid (**IIIbb**) was isolated as other major product in this case. In general, the coupling−cyclization reaction was carried out using 2 equiv of terminal alkynes (**II**). The use of a lesser amount, i.e. 1.5 equiv, of **II** also afforded **IV**, in good yields except in the case of **IIa**,**e**,**f**,**i**, where the corresponding products were isolated in low yields. Slow evaporation of **II** (due to the volatile nature of these alkynes) could be the reason for such observations. We next examined the possibility of using diversified *o*-iodobenzoic acids in this coupling−cyclization reaction. As expected, the substitutions on the benzene ring did not effect the reaction and, thus, isocoumarins bearing electron-donating and/or electron-withdrawing groups at the 5- and/or 7-positions of the aromatic ring were prepared in good yields (Table 3). The generality of this process was demonstrated further by synthesizing a 6,7-disubstituted isocoumarin in 70% yield (entry 7, Table 3).

The goal of this research was to develop an efficient and cheaper method for the synthesis of an isocoumarin library under mild and more environmental friendly conditions. We have addressed these issues partially by replacing the expensive palladium catalysts and solvent with less expensive 10% Pd/C and ethanol. Taking into consideration the scale-up potential of this process, we next examined the possibility of preparing isocoumarins by using this methodology in water. However, we failed to isolate the desired product when the reaction of **I** with terminal alkyne **IIa** was carried out in water instead of EtOH under the same reaction conditions as described above (entry 2, Table 1). The use of 2-aminoethanol in place of triethylamine afforded no isocoumarin or phthalide but a different coupled product, i.e., 2-((2-hydroxy-

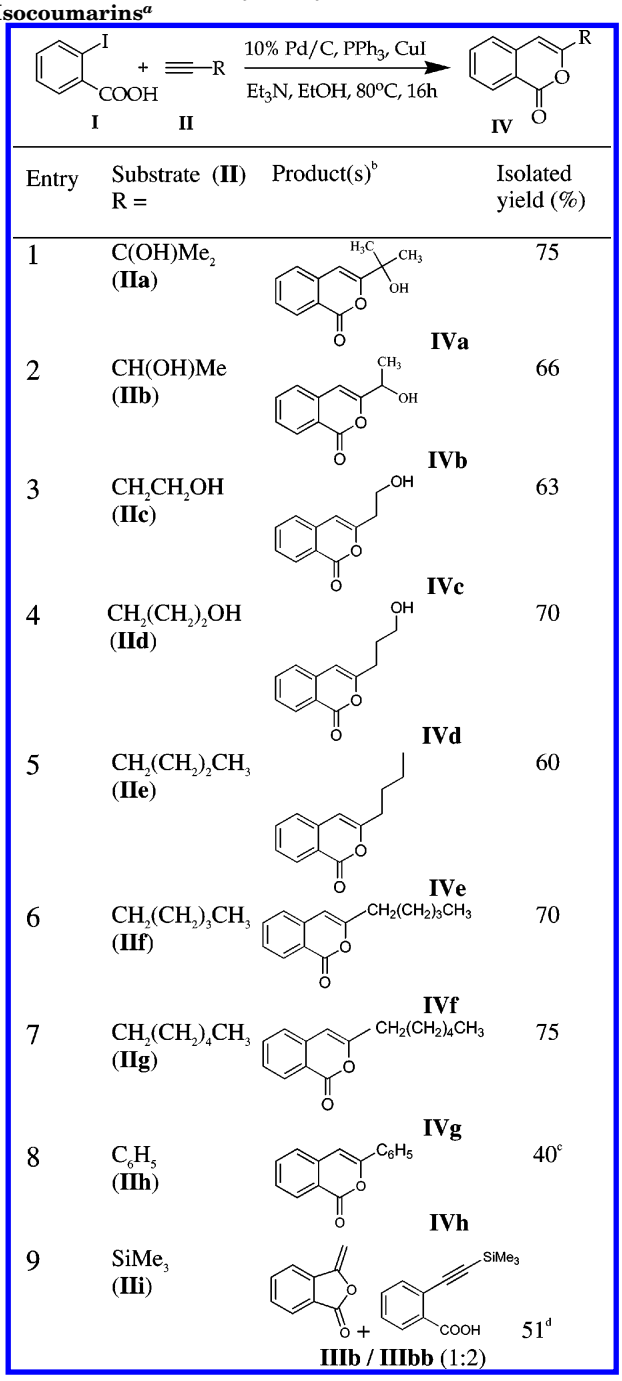
(16) (a) *o*-Iodobenzoic acid and all the terminal alkynes used are commercially available. (b) 5-Nitro-2-iodobenzoic acid was prepared via nitration of *o*-iodobenzoic acid according to the procedure described in the literature; see: Goldstein, H.; Grampoloff, A. V. *Helv. Chim. Acta* **1930**, *13*, 310−314. (c) 2-Iodo-3-methoxybenzoic acid was prepared via diazotization of 2-amino-3-methoxybenzoic acid according to the procedure described in the literature; see: Kenner, J.; Turner, H. A. *J. Chem. Soc.* **1928**, 2340−2343. For the preparation of 2-iodo-4,5-dimethoxybenzoic acid from 2-amino-4,5-domethoxybenzoic acid, see: Kundu, N. G.; Khan, M. W. *Tetrahedron* **2000**, *56*, 4777−4792. (d) The spectral and other characterization data for selected compounds are as follows. **IVa**: white solid; mp 66−68 °C (lit[10a] mp 70−72 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.27 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 6.5 Hz, 1H), 7.49−7.26 (m, 2H), 6.62 (s, 1H, CH=C), 1.99 (bs, 1H, OH), 1.60 (s, 6H, $2CH_3$); IR (KBr, cm^{-1}): 3381 (bs, OH), 1733 (C=O); mass (*m*/*z*) 204 (M^+, 50%), 189 (M^+ − 15, 100%); ^{13}C NMR (50 MHz, $CDCl_3$) 162.4 (C=O), 162.3, 137.2, 134.6, 129.2, 127.7, 125.7, 119.8, 99.7 (CH=C), 70.5 (CMe_2OH), 30.9 (CH_3), 28.1 (CH_3); UV (MeOH, nm) 323.0, 272.0, 263.0, 239.0, 228.0; HPLC 97.3%, column Inertsil ODS 3V (150 × 4.6) mm, mobile phase A 0.01 M KH_2PO_4, mobile phase B CH_3CN, gradient (*T*, °C/% B) 0/20, 3/20, 15/80, 20/80, 21/20, 22/20, flow rate 1.5 mL/min, UV 230 nm, retention time 8.4 min. **IVd**: white solid; mp 64−66 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.25 (d, J = 8.1 Hz, 1H), 7.69−7.65 (m, 1H), 7.48−7.44 (m, 1H), 7.35 (d, J = 8.1 Hz, 1H), 6.30 (s, 1H, CH=C), 3.75 (t, J = 6.2 Hz, 2H, CH_2), 2.67 (t, J = 7.5 Hz, 2H, CH_2), 2.02−1.95 (m, 2H, CH_2), 1.56 (1H, D_2O exchangeable, OH); IR (KBr, cm^{-1}) 3435 (bs, OH), 1738 (C=O), 1656; mass (*m*/*z*) 205 (M^+ + 1, 100%), 187 (M^+ − 18, 50%); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.2 (C=O), 157.4, 137.5, 134.7, 129.4, 127.6, 125.0, 120.0, 103.3 (CH=C), 61.5 (CH_2), 29.9 (CH_2), 15.7 (CH_2); UV (MeOH, nm) 326.0, 273.0, 264.0, 240.0, 229.0; HPLC 99.3%, Inertsil ODS 3V (150 × 4.6 mm) mobile phase A 0.01 M KH_2PO_4, mobile phase B CH_3CN, gradient (*T*, °C/% B) 0/25, 3/25, 12/80, 20/80, 21/25, 22/25; 1.5 mL/min, UV 230 nm, retention time 6.33 min. (e) For a similar coupling reaction of *o*-iodobenzoic acid with primary amine, e.g. L-valine, see: Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459−12467.

ethyl)amino)benzoic acid, within 2 h in 72% yield, presumably due to the increased nucleophilicity of the amine (see later for mechanistic discussion).[16e] The use of an inorganic base such as K_2CO_3 also failed to afford the desired product in aqueous media.

Mechanistically,[10,11] this reaction seems to proceed via in situ generation of 2-(1-alkynyl)benzoic acid in the presence of 10% Pd/C, PPh_3, and CuI, which in turn undergoes *6-endo-dig* cyclization[17] in a regioselective manner to give the six-membered isocoumarin. This was further supported by the isolation of **IIIbb** (entry 9, Table 2), where apparently the stability of the cationic intermediate and the steric bulk of the $SiMe_3$ group affected the cyclization of the coupled product (see later for mechanistic discussion). Recent studies[12a,18] have shown that the minor portion of the bound palladium (Pd/C) released into the solution is the actual catalytic species, indicating that the catalytic cycle works in solution rather than on the surface and the active species is a dissolved Pd−PPh_3 complex.[19] On the other hand, according to Amatore and Jutand,[20a,b] halide ions play a specific role in generating an anionic species such as $[L_2Pd^0Cl]^-$ from $Pd(PPh_3)_2X_2$, which is thought to be the active palladium species in the cross-coupling reactions.[20c] On the basis of this information a plausible mechanism is proposed in Scheme 1.

The anionic species $[(PPh_3)_2Pd^0I]^-$ (**X**) generated in situ from Pd/C and PPh_3 and then in the presence of CuI/terminal alkynes thus catalyzes the coupling of *o*-iodobenzoic acid with copper(I) acetylides (generated in situ from terminal alkynes) via intermediates[20d] **Y** and **Z**, leading to the formation of 2-(1-alkynyl)benzoic acid, which subsequently undergoes cyclization to yield the corresponding isocoumarin.[20e] The enhanced rate of reaction observed in the presence of excess LiCl can be explained by coordination of the chloride with palladium in the catalyst activation step to form a chloride-ligated zerovalent palladium species that subsequently catalyzes the coupling−cyclization reaction. In the presence of 2-aminoethanol the 18-electron complex **Y** (generated by the oxidative addition of the aryl iodide to the zerovalent anion **X** and in which the iodide ion, borne by the Pd(0), remains attached to the Pd(II) center) undergoes elimination of iodide ion to yield a neutral pentacoordinated complex. This complex affords 2-((2-hydroxyethyl)amino)-benzoic acid via reductive elimination, followed by the regeneration of the active palladium species **X**. For the

TABLE 2. Pd/C-Catalyzed Synthesis of 3-Substituted Isocoumarins[a]



Entry	Substrate (**II**) R =	Product(s)[b]	Isolated yield (%)
1	$C(OH)Me_2$ (**IIa**)	**IVa**	75
2	CH(OH)Me (**IIb**)	**IVb**	66
3	CH_2CH_2OH (**IIc**)	**IVc**	63
4	$CH_2(CH_2)_2OH$ (**IId**)	**IVd**	70
5	$CH_2(CH_2)_2CH_3$ (**IIe**)	**IVe**	60
6	$CH_2(CH_2)_3CH_3$ (**IIf**)	**IVf**	70
7	$CH_2(CH_2)_4CH_3$ (**IIg**)	**IVg**	75
8	C_6H_5 (**IIh**)	**IVh**	40[c]
9	$SiMe_3$ (**IIi**)	**IIIb / IIIbb** (1:2)	51[d]

[a] All reactions were carried out by using **I** (1.0 equiv), **II** (2.0 equiv), 1/4/2 ratio of 10%Pd/C, PPh_3, and CuI, Et_3N (5 equiv) in EtOH for 16 h. [b] Identified by ^1H NMR, ^{13}C NMR, IR, mass. [c] A side product, i.e., 3-phenyl-4-(phenylethynyl)isocoumarin, was isolated in 25% yield. [d] Overall yield.

(17) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−736. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736−738.

(18) Mori, Y.; Seki, M. *J. Org. Chem.* **2003**, *68*, 1571−1574.

(19) De la Rosa, M. A.; Velarde, E.; Guzman, A. *Synth. Commun.* **1990**, *20*, 2059−2064.

(20) (a) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314−321. (b) Amatore, C.; Jutand, A.; Khalil, F.; M'Barki, M. A.; Mottier, L. *Organometallics* **1993**, *12*, 3168. (c) The use of 4 equiv of PPh_3 was necessary to achieve the best catalytic activity of the Pd/C used. In addition to the other donors, i.e., Et_3N and EtOH, the excess of PPh_3 presumably interacted with the bound palladium that helped in releasing the portion of palladium into the solution. (d) The *σ*-coordinated benzoic acid in intermediates **Y** and **Z** may alternatively be represented by the structures shown below, taking into consideration of the fact that either of the carboxylic acid oxygens would form a perfect five-membered chelate, most likely displacing the extra iodide, as the binding strength of the chelate would be much greater than the Pd−I bond strength (we thank one of the reviewers for bringing this to our attention). In ethanol the intermediate **Z**, however, would afford 2-(phenylethynyl)benzoic ester as a main or side product in addition to the desired isocoumarins (**IV**) as shown below. Since this ester was never isolated even in trace quantity from the reaction mixture, the intermediacy of the chelated benzoic acid in **Y** and **Z** would seem to be unlikely. (e) Grosshenny, V.; Romero, F. M.; Ziessel, R. *J. Org. Chem.* **1997**, *62*, 1491−1500.

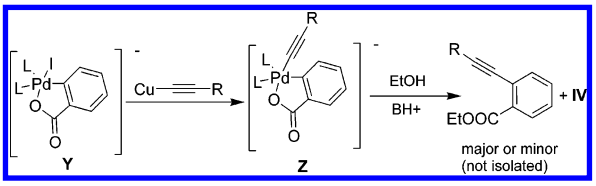
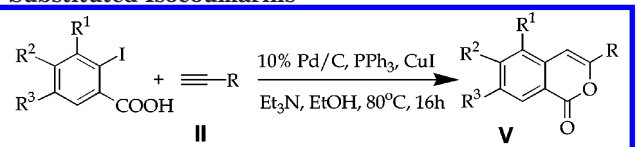
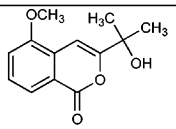
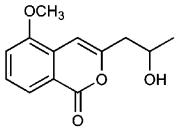
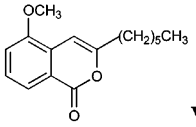
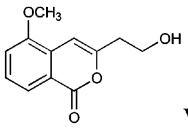
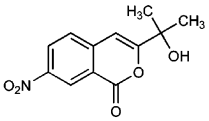
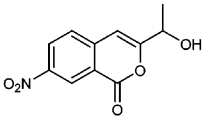
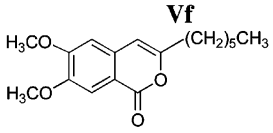


TABLE 3. Pd/C-Catalyzed Synthesis of Functionalized 3-Substituted Isocoumarins[a]

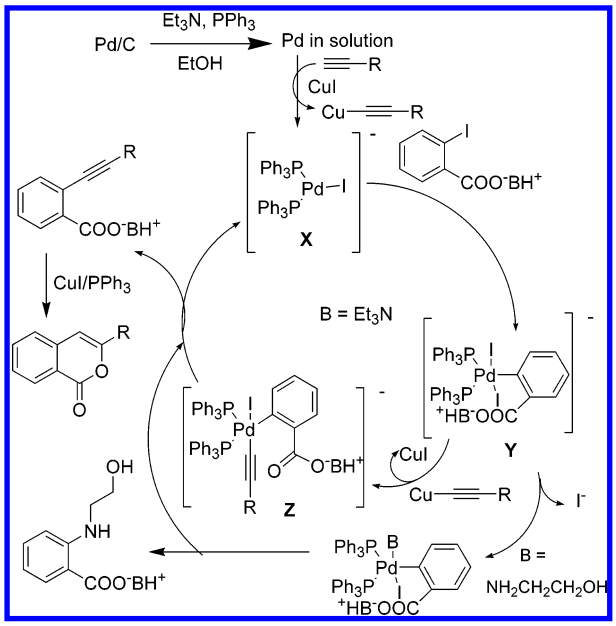


Entry	R^1; R^2	R^3	II	Products[b] (V)	Isolated yield (%)
1	OCH_3; H	H	IIa	 Va	76
2	OCH_3; H	H	IIj[c]	 Vb	70
3	OCH_3; H	H	IIg	 Vc	74
4	OCH_3; H	H	IIc	 Vd	78
5	H; NO_2	H	IIa	 Ve	66
6	H; NO_2	H	IIb	 Vf	60
7	H; OCH_3	OCH_3	IIg	 Vg	70

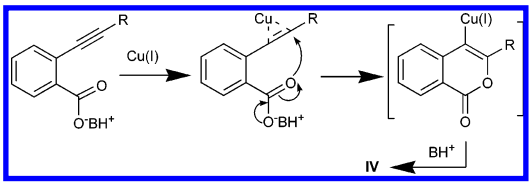
[a] For reaction conditions see footnote *a* in Table 2. [b] Identified by ^{1}H NMR, ^{13}C NMR, IR, mass. [c] For **IIj**, R = $CH_2CH(OH)CH_3$.

intramolecular cyclization of 2-(1-alkynyl)benzoic acid, the "6-*endo-dig*" or the "5-*exo-dig*" closure is allowed by Baldwin's rule. However, reasons for the observed regioselectivity associated with the use of 10% Pd/C−CuI−PPh_3 as a catalyst system are not yet clear at this stage. The direction of favored cyclization seems to be influenced greatly by the nature of the catalysts as well as solvent used in the present case. The 6-*endo-dig* cyclization was favored over 5-*exo-dig* closure in ethanol, possibly due to the higher stability of the six-membered cationic species in a polar protic solvent leading to the formation of endocyclic product (Scheme 2). However, to gain further evidence regarding the role of solvent in the present coupling−cyclization reaction 2-(phenylethynyl)-benzoic acid[21a] (known to be an intermediate in the palladium−copper-catalyzed coupling−cyclization of phenylacetylene with **I**)[10a] was treated with CuI−Et_3N−PPh_3

SCHEME 1. Plausible Mechanism for the Formation of Isocoumarin



SCHEME 2. Intramolecular Cyclization of 2-(1-Alkynyl)benzoic Acid



in EtOH and 1,4-dioxane separately at 80 °C for 2 h. The reaction in ethanol gave the corresponding isocoumarin in 70% yield, whereas a 1:1 mixture of phthalide and isocoumarin was isolated in 60% overall yield in 1,4-dioxane, indicating that the combined effect of CuI and PPh_3 was likely responsible for the preferred 6-*endo-dig* cyclization in ethanol. Notably, despite its well-known role in the formation of phthalides, Cu(I) salts are also known to catalyze the intramolecular cyclization of 2-(1-alkynyl)benzoic acid or its derivative to the six-membered lactone ring.[5b,9d,f,21b,c] The possibility of a Pd(II)-catalyzed cyclization of 2-(1-alkynyl)benzoic acid that usually affords isocoumarin as a predominant product[5f] can be ruled out, because the existence of such a species is unlikely under the reaction conditions studied. The participation of the anionic species **Y**, which contains a Pd(II) center and could catalyze the cyclization step to afford a 4-aryl-substituted isocoumarin, was also ruled out, because the corresponding product was not detected in the reaction mixture.

The structures of all 3-substituted isocoumarins were confirmed by satisfactory spectroscopic (MS, IR, and ^{1}H NMR) data. The isocoumarins can be differentiated from the corresponding phthalides (that are usually found to be side products in the other palladium-mediated syn-

(21) (a) This compound was prepared according to the procedure described in ref 10a. (b) For Cu(I)-catalyzed intramolecular cyclization of *o*-ethynylphosphonic acid monoesters to phosphaisocoumarins, see ref 8a and: (c) Ivanchikova, I. D.; Usubalieva, G. E.; Schastnev, P. V.; Moroz, A. A.; Shvartsberg, M. S. *Izv. Akad. Nauk*, *Ser. Khim.* **1992**, *9*, 2138−2146; *Chem. Abstr.* **1993**, *118*, 123864.

theses of isocoumarins) on the basis of several spectroscopic data, especially ^{1}H NMR and IR spectra. On the basis of the reported[10a] comparison between the six- and five-membered lactone rings of isocoumarins (ν_{max}(C=O) 1710−1750 cm^{-1} in IR and δ_H(vinylic) 6.3−7.0 in ^{1}H NMR spectra) and 3-ylidenephthalides (ν_{max}(C=O) 1770−1800 cm^{-1} in IR and δ_H(vinylic) 5.0−7.0 in ^{1}H NMR spectra), respectively, we found that our observations were in full agreement with the spectral data reported for isocoumarins.

We have shown that the Pd/C−Et_3N−PPh_3−CuI catalyst system allows smooth and effective coupling of 2-iodobenzoic acid with terminal alkynes. A detailed study on the methodology along with its limitations has also been described. In ethanol this catalyst system can be utilized for a practical, one-pot synthesis of isocoumarins. In contrast to the $PdCl_2(PPh_3)_2$−Et_3N−CuI system in DMF this process exhibited greater selectivity for isocoumarins. Moreover, unlike the $Pd(PPh_3)_4$−Et_3N−$ZnCl_2$ system the present methodology does not involve the use of expensive as well as air-sensitive palladium(0) catalyst and a substantial quantity of $ZnCl_2$. Since many terminal alkynes are commercially available or synthetically accessible, the described methodology, because of its operational simplicity, holds promise especially in the synthesis of isocoumarin-based molecules for thorough SAR studies in a medicinal chemistry setting. Of the several isocoumarins synthesized, 3-butylisocoumarin (**IVe**) is a precursor for a naturally occurring isocoumarin, i.e., artemidin,[5b] and compounds of biological interest.[22a,b] Moreover, it can be converted to the corresponding 3-substituted isoquinolone easily.[7d] 3-Pentylisocoumarin (**IVf**) showed significant antibacterial activity comparable to the standard antibiotics.[22c] Further application of this process to generate isocoumarin-based chemical libraries of potential pharmacological interest is currently underway.

Experimental Section

Typical Procedure for the Preparation of IVe. A mixture of **I** (0.3 g, 1.21 mmol), 10% Pd/C (35 mg, 0.033 mmol), PPh_3 (38 mg, 0.14 mmol), CuI (14 mg, 0.07 mmol), and Et_3N (0.61 g, 0.84 mL, 6.05 mmol) in EtOH (15 mL) was stirred at 25 °C for 30 min under nitrogen. The acetylenic compound **IIe** (0.199 g, 0.28 mL, 2.42 mmol) was added slowly with stirring. The mixture was then stirred at 80 °C for 16 h, cooled to room temperature, diluted with EtOAc (50 mL), and filtered through Celite. The filtrate was collected and concentrated. The residue was purified by column chromatography (petroleum ether−EtOAc) to afford the desired product (0.146 g, 60% yield).

Acknowledgment. We thank Dr. A. Venkateswarlu, Dr. R. Rajagopalan, and Prof. J. Iqbal for their encouragement and the analytical group for spectral support.

Supporting Information Available: Text giving experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050440E

(22) (a) Shafiq, Z.; Arfan, M.; Rama, N. H.; Hussain, M.; Hameed, S. *Indian J. Chem., Sect. B* **2003**, *42*, 1523−1526. (b) The 3-butyl side chain has been found to be a prerequisite for high antifungal activity of several naturally occurring isocoumarins; see: Engelmeier, D.; Hadacek, F.; Hofer, O.; Lutz-Kutschera, G.; Nagl, M.; Wurz, G.; Greger, H. *J. Nat. Prod.* **2004**, *67*, 19−25. (c) Rama, N. H.; Iqbal, R.; Zamani, K.; Saeed, A.; Iqbal, M. Z.; Choudhary, M. *Indian J. Chem., Sect. B* **1998**, *37*, 365−369.