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Pd(II)-Mediated Cyclization of *o*-Allylbenzaldehydes in Water: A Novel Synthesis of Isocoumarins

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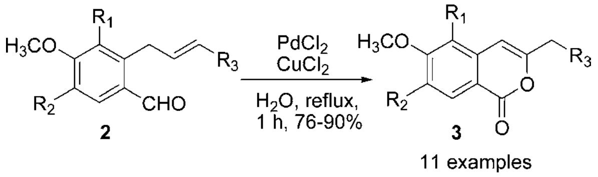
ABSTRACT



A novel, concise and efficient synthesis of substituted isocoumarins is disclosed. *o*-Allylbenzaldehydes prepared from isovanillin were mediated by $PdCl_2-CuCl_2$ in water to undergo a domino reaction sequence, including 6-*exo-trig* cyclization, the addition of water, the elimination of PdHCl, the isomerization of carbon–carbon double bond, the oxidation of hemiacetals with the elimination of PdHCl, and regeneration of $PdCl_2$ *in situ* to yield a series of new substituted isocoumarins in high yields, in one pot.

Isocoumarins, named 1*H*-isochromen-1-ones or 1*H*-benzopyran-1-ones, have attracted the attention of chemists due to their diverse biological activities including antioxidative,[1] antiangiogenic,[2] antifungal,[3] antiallergic, and antimicrobial activities;[4] the inhibition of such enzymes as human leukocyte elastase,[5] urokinase type plasminogen activator,[6] pancreatic cholesterol esterase,[7] and serine proteases;[8] and the inhibition of histamine release.[9] In addition to its natural occurrence,[10] a number of synthetic methods for isocoumarins were disclosed and initially reviewed by Barry in 1964.[11] At that time, the cyclization of homophthalic or methyl- benzoic acids was the most common synthetic strategy used. Interest in this class of compounds has not declined since. In 1997, 33 years later, the development of the synthesis of isocoumarins was comprehensively reviewed by Napolitano.[12] Over this period of time, the major synthetic methods included the reaction of methyl 2-allyl-2-iodobenzoate with internal alkynes in the presence of a Pd(0) catalyst,[13] the reaction

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of methyl benzoates in three steps (LiOH, $PdCl_2$, and then DEAD, PPh_3, and MeOH),[14] and the reaction of 2-benzoylbenzoic acids with ethyl bromomalonate in the presence of K_2CO_3 without isolation of the given intermediate, followed by cyclization in acidic conditions,[15] as well as others.[16] However, these methods suffered from several disadvantages such as the use of commercially inaccessible starting materials, tedious reaction conditions, substituent limitations, and lower yields. Most recently, numerous new and unique syntheses of isocoumarins have been disclosed such as the reaction of *o*-halobenzoic acids and 1,3-diketones via a CuI-catalyzed domino coupling/addition/deacylation process,[17] iridium-catalyzed oxidative lactonization, and intramolecular Tishchenko reaction of δ-ketoaldehydes,[18] the $FeCl_3$-promoted regioselective annulation of *o*-(1-alkynyl)benzoates with disulfides,[19] the reaction of α-diazophosphonates and *o*-formyl benzoic acids or *o*-(alkoxycarbonyl) benzoic acids catalyzed by rhodium acetate,[20] and the reaction of homophthalic anhydride with 2-methyl malonates in the presence of base.[21] Despite its numerous variations, intramolecular cyclizations catalyzed by Pd or other metals were generally designed as a catalysis for yielding isocoumarins. However, some of these methods also suffer from certain common problems such as the lack of chemical selectivity and the use of toxic organic solvents. Therefore, methods for reducing the competition of undesired cyclization and reducing or circumventing solvent wastes are urgently needed. To the best of our knowledge the use of Pd-catalyzed 6-*exo-trig* cyclization in water for the synthesis of isocoumarins has yet to be examined. Therefore, in this study, we thus report a novel synthetic method for isocoumarins via domino reactions including cyclization/addition/elimination/isomerization/oxidation/elimination/regeneration processes mediated by palladium(II) chloride and copper(II) chloride in water (Scheme 1). The advantage of our strategy is that it favors 6-*exo-trig* cyclization. Moreover, H_2O is used as both the reagent and the solvent which is atom-economical and safe for humans and the environment, and the reaction produces high yields in a short reaction time. In addition, the key intermediates **2a**–**j** were easily prepared from isovanillin.[22] To identify the optimum conditions for this cyclization, 2-allyl-3,4-dimethoxybenzaldehyde (**2a**) was studied under various conditions as a model reaction. The obtained results are provided in Table 1. As shown in Table 1, isocoumarin **3a** can be accessed (entry 1) by replacing H_2O with MeOH but its lower yield and the toxicity of MeOH are disadvantages. Using THF or CH_2Cl_2 as the reaction solvent (entries 2 and 3), no desired product was observed but the starting material was completely recovered. This result means that no reaction can occur at all in aprotic solvents such as THF or CH_2Cl_2. On the other hand, the use of $PdCl_2$ (0.5 equiv) and $CuCl_2$ (2 equiv) in water at reflux for 1 h (entry 4) is the optimum condition for 2-allyl-3,4-dimethoxybenzaldehyde (**2a**) to undergo 6-*exo-trig* cyclization to yield 5,6-dimethoxy-3-methyl-isocoumarin (**3a**). From comparison of the Pd catalysts for this cyclization, Pd(II) (e.g., $PdCl_2$ and $Pd(OAc)_2$) (entries 4,5, and 6) is observed to be far better than Pd(0) (e.g., $PdCl_2(PPh_3)_2$) (entry 7) or no Pd catalyst (entry 8). Thus, the trend for palladium catalysts is $PdCl_2 > Pd(OAc)_2 \gg PdCl_2(PPh_3)_2$. Three copper(II) salts, $CuCl_2$, $CuSO_4$, and $Cu(OAc)_2$, were investigated in

Scheme 1. $PdCl_2$–$CuCl_2$ Catalyzed the Synthesis of 3-Substituted Isocoumarins from *o*-Allylbenzaldehydes

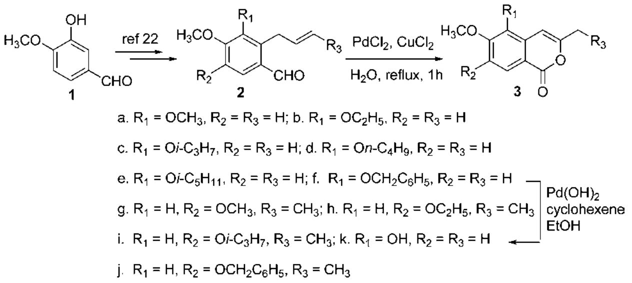
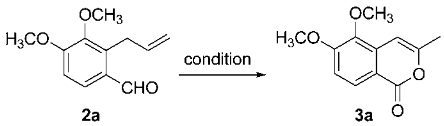


Table 1. Synthesis of Isocoumarin (**3a**) from 2-Allyl-3,4-dimethoxybenzaldehyde (**2a**) under Various Reaction Conditions[a]



entry	Pd (equiv)	Cu (equiv)	solvent	yield[b] (%)
1	$PdCl_2$ (0.5)	$CuCl_2$ (2)	CH_3OH	75
2	$PdCl_2$ (0.5)	$CuCl_2$ (2)	THF	0[c]
3	$PdCl_2$ (0.5)	$CuCl_2$ (2)	CH_2Cl_2	0[c]
4	$PdCl_2$ (0.5)	$CuCl_2$ (2)	H_2O	84
5	$PdCl_2$ (0.5)	$CuCl_2$ (1)	H_2O	71
6	$Pd(OAc)_2$ (0.5)	$CuCl_2$ (2)	H_2O	73
7	$PdCl_2(PPh_3)_2$ (0.5)	$CuCl_2$ (2)	H_2O	0[c]
8	none	$CuCl_2$ (2)	H_2O	0[c]
9	$PdCl_2$ (0.5)	$CuSO_4$ (2)	H_2O	66
10	$PdCl_2$ (0.5)	$Cu(OAc)_2$ (2)	H_2O	70

[a] Reaction conditions: Compound **2a** (0.42 g, 2.0 mmol), Pd catalyst, and Cu(II) suspended in solvent (30 mL) were heated to reflux for 1 h. [b] Isolated yield. [c] Recovery of starting material (100%).

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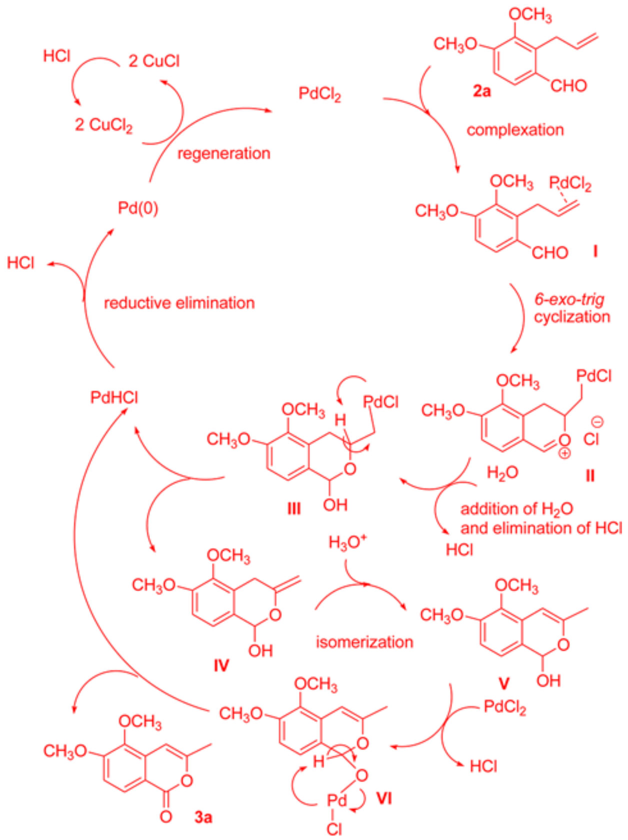
Scheme 2. Proposal Mechanism for the Formation of **3a** from **2a** Catalyzed by $PdCl_2-CuCl_2$ in Water



this cyclization. The trend for copper(II) salts is thus $CuCl_2$ > $Cu(OAc)_2$ > $CuSO_4$. The cited quantities of $PdCl_2$ (0.5 equiv) and $CuCl_2$ (2 equiv) are required for this optimum cyclization. Based on the experimental results, the reaction mechanism shown in Scheme 2 is proposed and illustrated as follows: (i) Complexation of $PdCl_2$ with the carbon–carbon double bond of **2a** yields transient **I**. (ii) The oxygen of the formyl group of transient **I** attacks the carbon–carbon double complex to undergo an intramolecular 6-*exo-trig* cyclization to give the oxonium transient **II**. (iii) Following the addition of water and the elimination of HCl, the hemiacetal transient **III** is produced. (iv) Subsequently, transient **III** undergoes elimination to yield transient **IV** and PdHCl. (v) The forming hemiacetal transient **IV** (two substituted olefin) is isomerized to the more stable transient **V** (three substituted olefin) in an acidic aqueous medium, and PdHCl undergoes reductive elimination to release Pd(0) and HCl. (vi) Pd(0) is recycled to $PdCl_2$ by $CuCl_2$, which is regenerated from the forming CuCl and HCl *in situ*. On the other hand, the transient **V** is further reacted with $PdCl_2$ to yield transient **VI** and HCl. And (vii) the oxidative elimination of transient **VI** gives the desired isocoumarin **3a**, together with PdHCl, which again joins the reaction cycle. In the case of MeOH (Table 1, entry 1), it reacts as a nucleophile to attack the oxonium transient **II** to yield acetal (**III-1**). Then, following the mechanism pathway of H_2O as a nucleophile, isocoumarin **3a** is yielded (shown in Scheme 3).

Scheme 3. Proposal Mechanism for the Formation of **3a** from **2a** Catalyzed by $PdCl_2-CuCl_2$ in MeOH

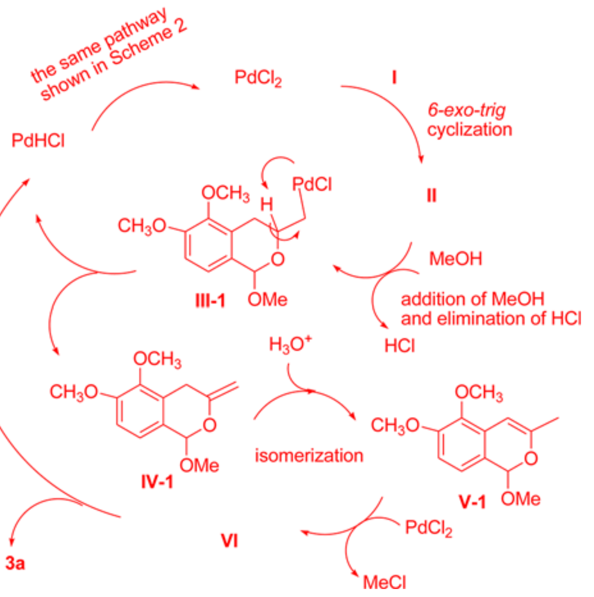
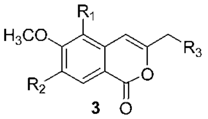


Table 2. % Yields of Isocoumarins (**3a**–**j**) Prepared from *o*-Allylbenzaldehydes (**2a**–**j**) Catalyzed by $PdCl_2-CuCl_2$ in Water, and Debenzylation of **3f** To Yield **3k**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a. $R_1 = OCH_3$, $R_2 = R_3 = H$; b. $R_1 = OC_2H_5$, $R_2 = R_3 = H$

c. $R_1 = O\textit{i}\text{-}C_3H_7$, $R_2 = R_3 = H$; d. $R_1 = O\textit{n}\text{-}C_4H_9$, $R_2 = R_3 = H$

e. $R_1 = O\textit{i}\text{-}C_5H_{11}$, $R_2 = R_3 = H$; f. $R_1 = OCH_2C_6H_5$, $R_2 = R_3 = H$

g. $R_1 = H$, $R_2 = OCH_3$, $R_3 = CH_3$; h. $R_1 = H$, $R_2 = OC_2H_5$, $R_3 = CH_3$

i. $R_1 = H$, $R_2 = O\textit{i}\text{-}C_3H_7$, $R_3 = CH_3$; k. $R_1 = OH$, $R_2 = R_3 = H$

j. $R_1 = H$, $R_2 = OCH_2C_6H_5$, $R_3 = CH_3$

$Pd(OH)_2$
cyclohexene
EtOH

compd	yield (%)	compd	yield (%)	compd	yield (%)
3a[a]	84	**3e**	83	**3i**	82
3b	90	**3f**	79	**3j**	76
3c	87	**3g**	81	**3k**	87
3d	86	**3h**	83		

[a] All isocoumarins prepared are new compounds except **3a**.

Based on the optimum conditions reported herein, isocoumarins (**3a**–**j**) were prepared from *o*-allylbenzaldehydes (**2a**–**j**) by $PdCl_2-CuCl_2$ in water through intramolecular cyclization, addition, oxidation, elimination, and isomerization. The debenzylation of **3f** to yield **3k** was also accomplished. All isocoumarin structures (**3a**–**k**) were supported by IR, ^{1}H NMR, ^{13}C NMR, HRMS spectral data, and elemental analysis. The yields of isocoumarins (**3a**−**j**) prepared from *o*-allylbenzaldehydes (**2a**−**j**) catalyzed by $PdCl_2$−$CuCl_2$ in water are provided in Table 2. Other selected physical and spectral data of **3a**−**k** are provided in Table 3 (available in the Supporting Information).

In summary, we have discovered a novel synthetic route to obtain isocoumarins in good yields. This domino reaction demonstrated that *o*-allylbenzaldehydes mediated by $PdCl_2$−$CuCl_2$ in water go through the following sequential steps: intramolecular cyclization catalyzed by palladium(II) chloride, nucleophilic addition of water, the elimination of PdHCl, the isomerization of the carbon−carbon double bond, oxidation of the hemiacetal by palladium(II) chloride with the elimination of PdHCl, and the recycling of $PdCl_2$ from PdHCl *in situ*. All isocoumarin structures (**3a**−**k**) are new compounds except for **3a** and were fully characterized and supported by spectral data. The conversion of the given isocoumarins to other benzoheterocyclic compounds and their biological screening are currently in progress.

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Supporting Information Available. General procedure for the preparation of compounds **3a**−**k**, and spectral data as well as copies of NMR spectra for all isocoumarins. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.