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Synthesis of Isocoumarins via Palladium Catalyzed Reactions of Methyl 2-(2',2'-Dibromovinyl)benzoates

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Abstract: 3-Substituted isocoumarins are synthesized in good to excellent yields via palladium catalyzed coupling of 2-(2',2'-dibromovinyl)benzoates and organostannanes. The process involves a Stille reaction, and a subsequent annulation reaction.

Keywords: Isocoumarin; Palladium; Stille Reaction; Annulation

Isocoumarins are a class of naturally occurring lactones which display a wide range of biological activities.[1,2] Because palladium catalyzed reactions usually employ mild reaction conditions, they offer attractive synthetic routes to isocoumarins. Earlier syntheses by Hegedus,[3] Izumi,[4] Yamanaka,[5] and Larock[6] involved palladium catalyzed formation of 2-alkenyl or 2-alkynylbenzoic acids, and a subsequent annulation. These methods suffered from either multistep reactions or the requirement for a stoichiometric amount of palladium. Heck[7] and Larock[8] also reported a method in which methyl 2-iodobenzoates were coupled with internal alkynes to generate 3,4-disubstituted isocoumarins. Cheng and co-workers[9] successfully synthesized 3-substituted isocoumarins from 2-iodobenzoic acids and terminal alkynes employing a palladium catalyst and zinc chloride. While alkyl- or alkenylalkynes coupled well, the coupling of arylalkynes often led to contamination by phthalides and/or byproducts resulting from the coupling of two molecules of the alkyne used.

During our study of Stille reactions of 1,1-dibromoalkenes,[10] we found that heating methyl 2-(2',2'-dibromovinyl)benzoate, an organostannane, tris(dibenzylideneacetone)dipalladium ($Pd_2[dba]_3$), and a weak ligand in a solvent of low polarity gave the corresponding 3-substituted isocoumarin in good yield (Equation 1). Further investigation established that best results were obtained when the reactions are run with tris(2-furyl)phosphine (TFP)[11] in toluene. The results are summarized in Table 1.

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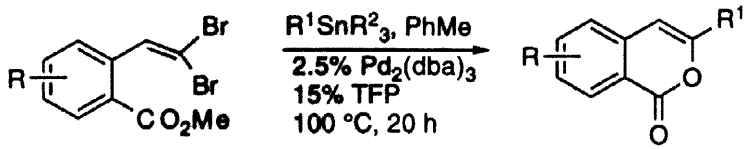
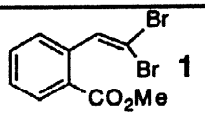
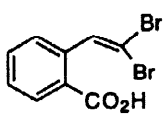
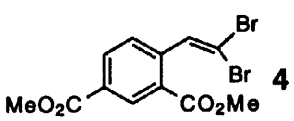
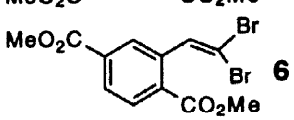
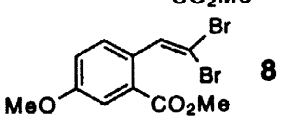
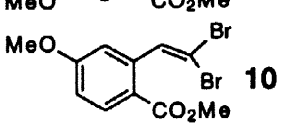


(1)

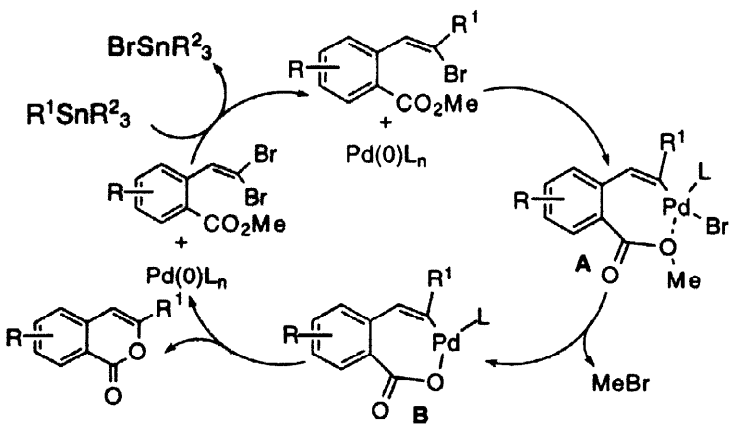
When vinyltributyltin was used (entry 5, Table 1), a poor yield of 3-vinylisocoumarin was obtained under the conditions optimized for arylstannane couplings. However, an improved yield was obtained when triphenylphosphine[12] was used in place of TFP. The reaction temperature was maintained at 100 °C or below, to prevent palladium(0) from precipitating.

Table 1. Syntheses of Isocoumarins

Entry	Vinyldibromide	$R^1SnR^2_3$	Product	Yield
1	 1	$PhSnMe_3$	**2a**	92%
2	**1**	2-Furyl$SnBu_3$	**2b**	85%
3	**1**	3-Furyl$SnBu_3$	**2c**	81%
4	**1**	2-Thienyl$SnBu_3$	**2d**	80%
5	**1**	Vinyl$SnBu_3$	**2e**	30%[a]
6	**1**	Vinyl$SnBu_3$	**2e**	52%[b]
7	 3	$PhSnMe_3$[c]	**2a**	59%
8	 4	$PhSnMe_3$	**5**	71%[d]
9	 6	$PhSnMe_3$	**7**	78%
10	 8	$PhSnMe_3$	**9**	81%
11	 10	$PhSnMe_3$	**11**	81%

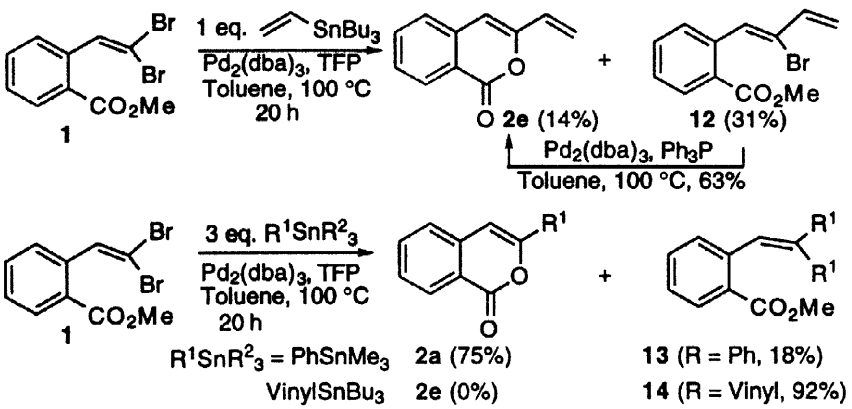
[a] The reaction was run for 48 h, and more catalyst ($Pd_2(dba)_3$/TFP) was added after 12 h. [b] The reaction was run with triphenylphosphine instead of TFP. [c] 2 Equivalents were used, as one equivalent of the stannane would be destroyed by the acid generated. [d] The reaction had to be run in 1,4-dioxane for reasons of solubility.

Scheme 1



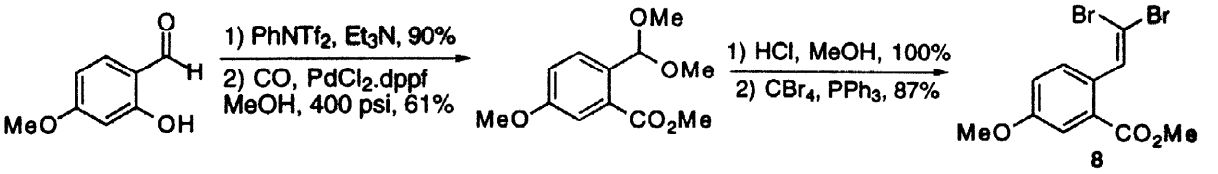
An abbreviated mechanism of the reaction is proposed in Scheme 1. The first step is a Stille reaction[13] of the *"E"* bromide with a stannane,[14] followed by the oxidative palladium insertion to the *"Z"* bromide to give intermediate **A**. Similar intermediates were proposed by both Heck[7] and Larock[15] for palladium catalyzed annulation reactions. The coordination of palladium to the ester group in **A** promotes the elimination of methylbromide to give intermediate **B**. Finally, reductive elimination gives the corresponding isocoumarin.

Scheme 2



Further evidence for the mechanism is shown in Scheme 2. When dibromide (**1**) was reacted with vinyltributyltin, the intermediate product **12** resulting from the Stille reaction was isolated, and then converted to isocoumarin **2e** in good yield. When excess trimethylphenyltin was used, a mixture of both the corresponding isocoumarin (**2e**) and the disubstituted product (**13**) was obtained. Because of the fast transmetallation rate of vinyltributyltin[12], only divinylation (**14**) was observed when vinyltributyltin was used.

The starting vinyldibromides could be readily synthesized from commercially available starting materials. The synthesis of **8** is a typical example, as shown below.



In summary, a novel method for efficient preparation of 3-substituted isocoumarins is described. Investigation to broaden the scope of this type of tandem Stille reaction and annulation is underway.

A representative reaction procedure follows: A solution of vinyldibromide **1**[16] (320 mg, 1.0 mmol), trimethylphenyltin (264 mg, 1.05 mmol), $Pd_2(dba)_3$ (23 mg, 0.025 mmol), TFP (35 mg, 0.15 mmol) in toluene (5 mL) was stirred at 100 °C under nitrogen for 20 hours. The reaction mixture was then filtered through a plug of silica gel, rinsed with ether, and concentrated. The residue was purified by silica gel column chromatography, eluting with 80:15:5 of hexane/dichloromethane/ethyl acetate to give **2a** as a white solid (204 mg, 92% yield).

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