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Palladium-catalyzed cross-coupling of 2-haloselenophene with terminal alkynes in the absence of additive

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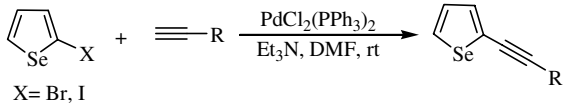
Abstract—We present herein our results of the Sonogashira coupling reaction of 2-haloselenophenes with terminal alkynes catalyzed by $PdCl_2(PPh_3)_2$, under co-catalyst free conditions and establish a new procedure to prepare (2-alkynyl)-selenophenes in good yields. The reaction proceeded cleanly under mild reaction conditions and was performed with propargylic alcohols, protected propargylic alcohols, propargylic amines, as well as alkyl, and aryl alkynes, in the presence of $PdCl_2(PPh_3)_2$, Et_3N, DMF, and in the absence of any supplementary additives. In addition, by this protocol (2,5-bis-alkynyl)-selenophenes were also obtained, in a one pot procedure, using 2,5-bis-iodoselenofene with an excess of terminal alkynes.

In the last decade, there have been developments in palladium-catalyzed coupling systems as a consequence of the great interest in the development of coupling substrates that are more economic, more easily accessible, and reactive even under mild conditions. In this way, the palladium-catalyzed cross-coupling reactions of aryl halides or triflates with terminal alkynes, commonly referred to as Sonogashira reactions, are a powerful, versatile and popular tool for selective construction of the new carbon–carbon bonds.[1] This reaction is generally co-catalyzed by copper salts and an amine as base and a phosphine as a ligand for palladium are also typically included. Recent advances of Sonogashira reactions, including the development of conditions with metals other than palladium[2] and a copper-free protocol[3] have been described. However, to the best of our knowledge, the efficiency of palladium catalyzed reaction of 2-haloselenophene with terminal alkynes, in the absence of co-catalyst and ligand has not been demonstrated. Our continuing interest in the synthesis[4] and applications[5] of organochalcogenides in organic synthesis prompted us to examine a procedure to prepare 2-(alkynyl)-selenophenes substituted by the palladium cross-coupling reaction of 2-haloselenophene with terminal alkynes (Scheme 1).[6]

Organoselenium compounds have become attractive synthetic targets because of their chemo-, regio-, and stereoselective reactions and their useful biological activities.[7] Furthermore, organoselenium compounds can usually be used in a wide variety of functional groups, thus avoiding protection group chemistry.[8] Organoselenium chemistry developed rapidly, mainly in the area of selenocarbohydrates, selenoamino acids, and selenopeptides. The selenium group can be introduced in an organic substrate via both nucleophile and electrophile reagents. After being introduced in an organic substrate, the organoselenium group can easily be removed by selenoxide *syn* elimination[9] and [2,3] sigmatropic rearrangement.[10] In addition, the carbon–selenium bond can also be replaced by a carbon–hydrogen,[11] carbon–halogen,[12] carbon–lithium,[13] or carbon–carbon bond.[14]



X= Br, I

Scheme 1.

Keywords: Selenides; Palladium cross-coupling; Selenophene.
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For preliminary optimization of the reaction conditions, we chose iodo-selenophene **1**[15] and propargyl alcohol **2a** as a model. In this way, a mixture of 2-iodo-selenophene (0.5 mmol), propargyl alcohol (0.5 mmol), and triethylamine (1 mmol) in dioxane was treated, at room temperature, with different palladium catalysts (Table 1).

As shown in Table 1, all Pd(0) and Pd(II) with different ligands tested, exhibit a good catalytic activity in this reaction (Table 1, entries 2–5), the exception was for $PdCl_2$ that gave unsatisfactory yield of the desired product **3a**, even so using CuI as a co-catalyst (Table 1, entry 1). Although it was found that the product yield was 95% in the presence of $PdCl_2(PPh_3)_2$ and CuI (Table 1, entry 5), in the presence of $PdCl_2(PPh_3)_2$ but in the absence of CuI it was 98% (Table 1, entry 6). This indicated that CuI was not essential as a co-catalyst in this reaction. It is important to note that when the amount of catalyst is reduced from 10 to 1 mol % a decrease in the yield was observed. Finally, we observed that when the reaction was run either in the absence of $PdCl_2(PPh_3)_2$ but in the presence of CuI (Table 1, entry 9) or in the absence of both $PdCl_2(PPh_3)_2$ and CuI (Table 1, entry 10), the desired product was not observed.

We also investigated the solvent influence, and we found that the yield of 2-ynyl-selenophene **3a** was markedly decreased using MeOH, CH_3CN, THF, CH_2Cl_2, or hexane, instead of DMF as the solvent.

Regarding the influence of the base in this coupling reaction, optimal results were achieved using triethylamine. By using pyrrolidine, piperidine or morpholine, moderate yields were obtained, while with inorganic bases, such as K_3PO_4, NaOH, K_2CO_3, Cs_2CO_3, Na_2CO_3, and EtONa no reaction was observed.

Thus, the careful analysis of the optimized reaction revealed that the optimum condition for this coupling was the use of $PdCl_2(PPh_3)_2$ (10 mol %), DMF (5 mL), iodo-selenophene **1** (0.5 mmol), propargyl alcohol **2a** (1.5 mmol), and Et_3N (1 mL), at room temperature for 24 h.

In order to demonstrate the efficiency of this reaction, we explored the generality of our method extending the conditions to other terminal alkynes and the results are summarized in Table 2.

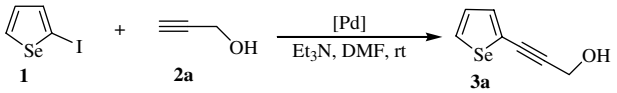
Inspection of Table 2 shows that the reaction worked well for a variety of propargylic alcohols. Both hindered and nonhindered propargyl alcohols gave the desired substituted selenophene in good yields (Table 2, entries 1–6). Our experiments showed that the reaction with terminal alkynes having either protected propargylic alcohols (Table 2, entry 7) or propargylic amines (Table 2, entries 8 and 9) also gave the coupled product in good yields, although the yield was lower than nonprotected propargylic alcohols. When we performed this reaction with aryl alkynes no obvious differences was found between electron-withdrawing and electron-donating substituents. These results demonstrated that the efficiency of the substituted selenophene formations cannot significantly depend on the electronic effects of the substituents in the aromatic ring (Table 2, entries 10–12). Checking Table 2, we also observed that the reaction worked well with alkyl alkynes providing 2-alkynil-selenophene substituted in moderated yields (Table 2, entries 14–16). Finally, it is worth mentioning that, through our methodology, it was possible to prepare the dual cross-coupled product, in a one pot procedure, in good yield, using ethyne gas (Table 2, entry 17).

Having optimized the reaction conditions for 2-iodo-selenophene we turned our attention to 2-bromo-selenophene.[17] The reaction was carried out using the standard reaction condition applied to 2-iodo-selenophene. As shown in Table 3, the reaction works well for propargylic alcohols, propargylic amines and aryl alkynes, however, the yield decreased when alkyl alkyne was used.

Finally, the possibility of generating 2,5-bis-acetylenic-selenophenes was also investigated. As illustrated in Table 4, the cross-coupling reaction of 2,5-diiodo-selenophene **4**[16] and terminal alkynes, under the same reaction conditions described for 2-iodo-selenophene, led to the substituted diacetylenic selenophenes derivatives **5a–c** in excellent yields (Table 4). We investigated the optimum conditions and found that there were necessary six instead of three equivalents of 1-alkyne to give the dual Sonogashira coupling in 2,5-diiodo-selenophene **4** (Table 4).

Plausible mechanism: In the absence of CuI we believed that active Pd(0) species (**B**) was produced via a reductive-elimination from the bis(triphenylphosphine)-dialkynylpalladium (**A**), which was derived from 1-alkyne and $Pd(PPh_3)_2Cl_2$ in the presence of triethylamine (Scheme 2). This reductive-elimination also generates the small amount of undesired homocoupling product that was always observed as the by-product. As shown in Scheme 2, the oxidative addition of 2-halo-selenophene to the active Pd(0) species (**B**) and subsequent

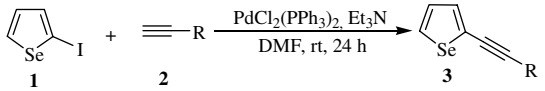
Table 1. Study of catalyst effect on the coupling reaction of 2-iodo-selenophene and propargyl alcohol



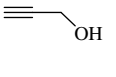
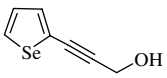
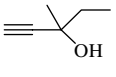
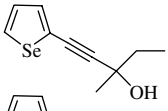
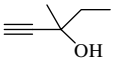
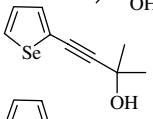
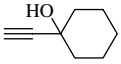
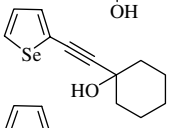
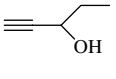
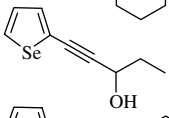
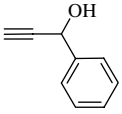
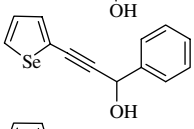
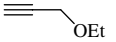
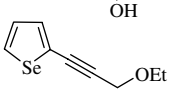
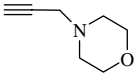
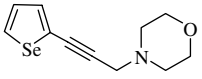
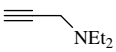
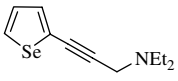
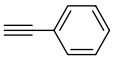
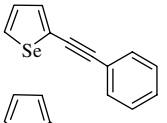
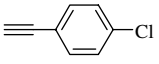
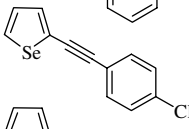
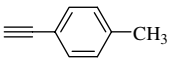
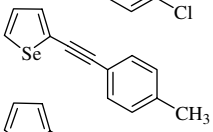
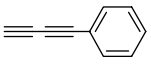
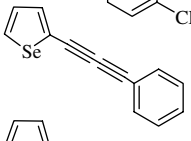
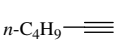
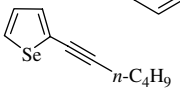
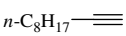
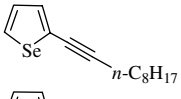
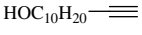
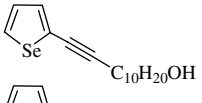
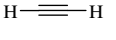
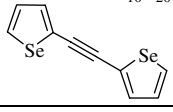
Entry	Catalyst (mol %)	CuI (mol %)	Yield[a] (%)
1	$PdCl_2$ (10)	10	25
2	$PdCl_2(PhCN)_2$ (10)	—	76
3	$Pd(PPh_3)_4$ (10)	10	95
4	$Pd(PPh_3)_4$ (10)	—	75
5	$PdCl_2(PPh_3)_2$ (10)	10	95
6	$PdCl_2(PPh_3)_2$ (10)	—	98
7	$PdCl_2(PPh_3)_2$ (5)	—	54
8	$PdCl_2(PPh_3)_2$ (1)	—	Traces
9	—	10	—
10	—	—	—

[a] Yields are given of isolated products by flash chromatography.

Table 2. Sonogashira coupling reaction of 2-iodo-selenophene and terminal alkynes

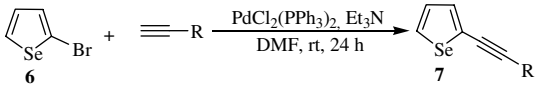


1 **2** **3**

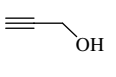
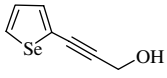
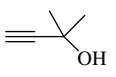
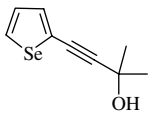
Entry	Alkyne	Product	Yield[a] (%)
1			98
2			88
3			98
4			98
5			86
6			64
7			55
8			67
9			60
10			85
11			91
12			88
13			65
14			49
15			50
16			65
17			50

[a] Yields are given of isolated products by flash chromatography.

Table 3. Sonogashira coupling reaction of 2-bromo-selenophene and terminal alkynes



6 **7**

Entry	Alkyne	Product	Yield[a] (%)
1			78
2			93
3			50
4			45
5			85
6			81
7			88
8			20

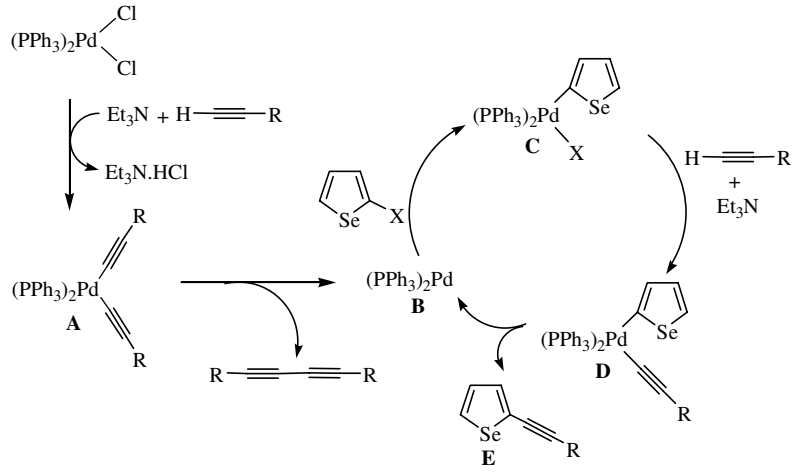
[a] Yields are given of isolated products by flash chromatography.

Table 4. Sonogashira coupling reaction of 2,5-diido-selenophene and terminal alkynes[a]

4 **5**

[a] Yields are given of isolated products by flash chromatography.

reaction with a terminal alkyne leads to the alkynyl-palladium(II) derivatives (**D**), which gives the coupled products 2-ynyl-selenophenes (**E**) and regenerates the active Pd(0) specie.



Scheme 2.

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2006.01.118.

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