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To cite this version:

HAL Id: hal-01501260
https://hal-univ-rennes1.archives-ouvertes.fr/hal-01501260
Submitted on 4 Jul 2017

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Unprecedented access to β-arylated selenophenes via palladium-catalysed direct arylation

Aymen Skhiri,[a,b] Ridha Ben Salem,[b] Jean-François Soulé,[b] and Henri Doucet*[a]

Abstract: Several methods allow the access to α-arylated selenophenes; whereas the synthesis of β-arylated selenophenes remains very challenging. We demonstrated that the Pd-catalysed coupling of benzenesulfonyl chlorides with selenophenes affords regiospecifically the β-arylated selenophenes. The reaction proceeds with easily accessible catalyst, base and substrates, and tolerates a variety of substituents both on the benzene and selenophene moieties. This transformation allows the programmed synthesis of polyarylated selenophenes with potential applications in pharmaceutical and material chemistry, as the installation of aryl groups at the desired positions can be achieved.

(Hetero)arylated selenophenes are important structures with several applications such as in the fields of pharmaceutical chemistry and organo-electronics.[1] If the biological or physical properties of several 2-(hetero)aryl selenophenes have been studied in detail, on the other hand, 3-arylselenophenes have attracted less attention. This is certainly due to the lack of convenient synthetic methods for the preparation of such structures.[2] Currently, β-arylated selenophenes can be prepared via Suzuki coupling using 3-bromoselenophene derivatives[3] (Scheme 1) or via Negishi coupling.[4]

Pd-catalysed β-arylations via Suzuki coupling

Scheme 1. Reported pathways for the synthesis of β-arylated selenophenes from selenophenes.

Since one decade, the metal-catalysed functionalization of C-H bonds has emerged as a very powerful method for the simpler access to molecules useful to materials or biological applications. 1 specific C–H bonds of (hetero)arenes can be coupled with arynes, providing one of the simplest ways for access to bi(hetero)aryls.[5] From thiophene derivatives, by tuning the reaction conditions, both the α- and β-arylated thiophenes can be easily obtained using Pd catalysed direct arylation.[6] In contrast, relatively little effort has been expended toward developing such metal-catalysed direct arylation for the synthesis of arylated selenophenes. In 2008, Mor Koumura et al. reported the first Pd-catalysed direct arylation of selenophene derivative (Scheme 2, top). Using aryl iodides as aryl source and PdCl2(PPh3)2 catalyst, they obtained regioselectively the C5-arylated 2-formylselenophenes.[7] Then, in 2014, Schneider et al. reported a condition allowing the access to 2-arylselenophenes from selenophene and aryl halides (Scheme 2, middle). To our knowledge, the metal-catalysed direct arylation at β-position of selenophene has not been reported so far (Scheme 2, bottom).[8] Therefore, it was of particular interest to us to achieve an arylation at the 3- or 4- positions of selenophenes.

Dong et al. reported in 2009 an example of Pd-catalysed direct arylation, via a desulfitative coupling, of a quinoline using p-TolSOCl as aryl source.[9,10] Following this seminal result, the use of ArSO2Cl as aryl source for the Pd-catalysed direct arylation has been extended to a variety of heteroarenes by several groups.[11,12] In 2014, we described a novel access to β-arylated thiophenes from thiophenes and ArSO2Cl, using desulfitative Pd-catalysed direct arylation.[13] However, to our knowledge, the desulfitative direct arylation of selenophenes with ArSO2Cl has not been reported.

Herein, we describe an environmentally benign general protocol allowing the completely regioselective access to β-arylated selenophenes, using Pd-catalysed desulfitative direct arylation, from selenophenes and ArSO2Cl (Scheme 2, bottom). The influence of

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[***] We thank the CNRS, Rennes Metropole and Scientific Ministry of Higher Education and Research of Tunisia for providing financial support.

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Scheme 2. Pd-catalysed direct arylation of selenophenes.
the ArSO\textsubscript{2}Cl and selenophenes substituents is reported. The high yielding programmed synthesis of a tetraaryl selenophene is also described.

Based on our previous results as a starting point,\textsuperscript{14-16} we first examined the influence of several reaction conditions on the product formation for the reaction of 1.5 equiv. of 4-nitrobenzenesulfonyl chloride with selenophene at 140 °C during 4 h (Scheme 3 and Table 1 in SI). Using 10 mol% Pd(OAc\textsubscript{2}) catalyst and 3 equiv. of Li\textsubscript{2}CO\textsubscript{3} as the base in 1,4-dioxane, the C3-arylated selenophene 1\textsubscript{a} was regiospecifically obtained in 56% yield. No formation of the C2-arylated selenophene derivative 1\textsubscript{b} was observed by GC/MS and \textsuperscript{1}H NMR analysis of the crude mixture. The use of PdCl\textsubscript{2}(C\textsubscript{6}H\textsubscript{5})(dpdb), PdCl\textsubscript{2}, PdCl\textsubscript{2}(MeCN)\textsubscript{2} or Pd(PPh\textsubscript{3})\textsubscript{4} catalysts also led regiospecifically to product 1\textsubscript{a}, but in lower yields. On the other hand, in the presence of a larger excess (6 equiv.) of Li\textsubscript{2}CO\textsubscript{3} base, product 1\textsubscript{a} was obtained 79% yield. Then, we examined the influence of other bases such as Na\textsubscript{2}CO\textsubscript{3}, K\textsubscript{2}CO\textsubscript{3}, Cs\textsubscript{2}CO\textsubscript{3}, K\textsubscript{3}PO\textsubscript{4} or KOAc; however, lower yields in 1\textsubscript{a} were obtained.

**Scheme 3.** Influence of the reaction conditions.

Then, the influence of the para-substituents on ArSO\textsubscript{2}Cl for reaction with selenophene was examined using 10 mol% Pd(OAc\textsubscript{2}) catalyst and 6 equiv. of Li\textsubscript{2}CO\textsubscript{3} in dioxane (Scheme 4). First we employed electron-deficient ArSO\textsubscript{2}Cl. Cyano- and trifluoromethyl-substituents on ArSO\textsubscript{2}Cl gave regiospecifically the C3-arylated selenophenes 2 and 3 in 88% and 83% yields, respectively. Relatively good yields were also obtained for the coupling of 4-chloro and 4-fluoro-benzenesulfonyl chlorides with selenophene, as the desired products 4 and 5 were isolated in 57% and 72% yields, respectively. It should be noted that no cleavage of the C-Cl bond was observed allowing further transformations. Good yields of 71% and 73% in 6 and 7 were also obtained from PhSO\textsubscript{2}Cl and p-TolSO\textsubscript{2}Cl; whereas, lower yields of 54% and 31% in 8 and 9 were produced from the electron-rich 4-tert-butyl- and 4-methoxy-benzenesulfonyl chlorides. The influence of meta-substituents on the ArSO\textsubscript{2}Cl partner was also evaluated. ArSO\textsubscript{2}Cl bearing CF\textsubscript{3}, Cl or F meta-substituents were successfully coupled with selenophene, affording regiospecifically the desired C3-arylated selenophenes 10-12 in 74-82% yields. ArSO\textsubscript{2}Cl containing two CF\textsubscript{3}, Cl or F substituents also gave the expected products 13-15 in good to high yields; whereas, the electron-rich 3,4-dimethoxy-benzenesulfonyl chloride afforded 16 in only 24% yield. ArSO\textsubscript{2}Cl containing cyano or chloro ortho-substituents were also tolerated affording 18 and 19 in 88% and 76% yields, respectively; whereas a nitro ortho-substituent gave 17 in only 31% yield. Polyfluorinated molecules are ubiquitous in medicinal chemistry, owing to fluorine atom properties which induce a dramatic change in the molecules behaviour. The use of ArSO\textsubscript{2}Cl containing fluorine atoms should offer a straightforward route to (poly)fluorinated 3-arylselenophenes. Indeed, from ArSO\textsubscript{2}Cl containing one to three fluoro substituents, the 3-arylselenophenes 21-23 were produced in 86-90% yields.

As the use of ArSO\textsubscript{2}Cl as coupling partners in Pd-catalysed direct arylation tolerates bromo and iodo substituents,\textsuperscript{14-16} the behaviour of several (poly)halobenzenesulfonyl chlorides for coupling with selenophene was investigated (Scheme 5). Satisfactory yields in 24 and 25 were obtained in the presence of ArSO\textsubscript{2}Cl containing 2- or 4-bromo-substituents. An addition ortho-ethyl-substituent exhibits a minor influence, as with 2-ethyl-4 bromobenzenesulfonyl chloride, a high yield of 74% in the target product 26 was obtained. 2-Bromobenzenesulfonyl chloride bearing CF\textsubscript{3} or F substituents also led to the expected 3-arylated selenophenes 27-29 in 75-83% yield. The reactivity of two dibromobenzenesulfonyl chlorides, which can be easily obtained by reaction of dibromobenzenes with chlorosulfonic acid, is also described in the scheme 5. In both cases, the target products 30 and 31 were obtained in good yields, without cleavage of both C-B bonds. Then, although C-I bonds on benzene rings are known to be very reactive in the presence of palladium catalysts, we examine the reactivity of 4-iodobenzenesulfonyl chloride in the presence of selenophene. The reaction affords 32 in only 33% yield, but without cleavage of the C-I bond.
The regioselectivity of the arylation of 2- or 3-substituted selenophenes was also determined (Scheme 6). We first examined the reactivity of 2-aryl selenophenes, which could be easily obtained via direct arylation of selenophene by aryl bromides using reported conditions. High yields in [33-36] were obtained from four 2-arylselenophenes using CF₃- or MeO-substituted ArSO₂Cl as aryl source. In all cases, a complete regioselectivity in favour of the arylation at C4-position of the 2-arylselenophene was observed. A bromo-substituent at C2-position on selenophene was also tolerated, affording the 4-aryl-2-bromoselenophenes 37-39 in 61-70% yields, without cleavage of the selenophenyl C-Br bond. Moreover, in the presence of 3,4-dibromobenzensulfonyl chloride and 4-iodobenzensulfonyl chloride, the 4-arylated 2-bromoselenophene derivatives 40 and 41 were obtained in moderate yields, but without cleavage of the C-halo bonds on both coupling partners. The reaction of 3-(4-methoxyphenyl)selenophene 9 with 4-nitrobenzensulfonyl chloride regioselectively affords the 3,4-diarylselenophene 42, which contains two different aryl groups, in 62% yield (Scheme 6, bottom). It was also possible to directly prepare the 3,4-diarylselenophene 43, bearing two identical aryl groups, by reaction of selenophene with 3 equiv. of benzenesulfonyl chloride derivative.
Scheme 7. Programmed polyarylations of selenophene.

Although the mechanism cannot yet be elucidated, a catalytic cycle shown on scheme 8 can be proposed. The first step is probably the oxidative addition of the ArSOCl to Pd(II) to afford the Pd(IV) intermediate A as for Dong reaction.\[^{10}\] Then, after elimination of SO₂, the coordination of selenophene gives B, which affords C after migration of the aryl group to the β-carbon atom of selenophene.\[^{15}\]

Finally, base-assisted proton abstraction gives the β-arylated selenophene with regeneration of the Pd(II) species. However, an Heck-type Pd(0)/Pd(II) mechanism, with carbo-palladation followed by an anti-β-hydride elimination or a base-assisted E2 elimination is also possible.\[^{16}\]

Scheme 8. Proposed catalytic cycle

In summary, we report here the first procedure promoting the hard-to-achieve arylation at β-position of selenophene derivatives. The reaction proceeds with easily accessible phosphine-free Pd(OAc)₂ catalyst and Li₂CO₃ as base and tolerates a wide variety of substituents both on the ArSOCl and selenophene coupling partners. Moreover, this procedure allows the programmed synthesis of polyarylated selenophenes as the installation of aryl groups at the desired positions can be achieved. Due to the wide availability of diversely functionalised ArSOCl, this strategy (no expensive base and ligand) should be very attractive to synthetic or material chemists for access to β-arylated and polyarylated selenophenes.

Keywords: Palladium · catalysis · C-H functionalization · selenophenes · benzenesulfonyl chlorides


Unprecedented access to $\beta$-arylated selenophenes via palladium-catalysed direct arylation.

The palladium-catalysed coupling of benzenesulfonyl chlorides with selenophene derivatives allows the access to $\beta$-arylated selenophenes with complete regioselectivity. The reaction proceeds with easily accessible catalyst, base and substrates, without oxidant and tolerates a variety of substituents both on the benzene and selenophene moieties.