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Tetrahedron Letters xxx (2014) xxx-xxx

Contents lists available at ScienceDirect



Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Palladium-catalyzed direct thiolation of ethers with sodium sulfinates

Shengrong Guo^{a,b}, Weimin He^a, Jiannan Xiang^{a,*}, Yanqin Yuan^{b,*}

^a College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, PR China
^b Department of Chemistry, Lishui University, 323000 Lishui, PR China

ARTICLE INFO

A B S T R A C T

in moderate to good yields.

Article history: Received 5 August 2014 Revised 8 September 2014 Accepted 22 September 2014 Available online xxxx

Keywords: Thiolation Sodium sulfinates Sulfides Pd(OAc)₂ Ethers

The direct functionalization of C–H bonds is of great importance to organic chemistry because of its high efficiency and high atom-economy.¹ Owing to their low reactivity, direct and selective methods of $C(sp^3)$ –H bond functionalization are challenging.² In recent years, however, much progress has been made in the area of oxidative functionalization of $C(sp^3)$ –H bonds to form C–C and C–X (X = O, N, S) bonds.³

Organosulfur compounds are of great importance to the pharmaceutical industry, material science, and general organic synthesis.⁴ With the development of direct C—H functionalization, remarkable progress has been made in the area of C—S bond formation.⁵ The first example of copper salt catalyzed thiolation of a C(sp²)—H bond was reported by Yu in 2006,^{5a} Subsequently, many thiolating reagents like disulfides,^{5c-f} S-arylthiophthalimides,⁶ sulfonyl hydrazides,⁷ sulfonyl chlorides,⁸ and mesitylphenyl sulfides⁹ have been used for direct arylthiolation of benzoxazole, benzothiazole, and indole in the presence of different metal catalysts. However, the selective thiolation of sp³-hybridized C—H bonds in simple ethers has remained a challenging task.

Recently, Deng^{5j} reported thiolation of indoles using sodium sulfinates, which are usually used in arylations, as an effective sulfur electrophiles and aryl thiol surrogate (Scheme 1a). Our group is interested in arylthiolation of sp³-hybridized C—H bonds.^{5e,10} To

* Corresponding authors.

http://dx.doi.org/10.1016/j.tetlet.2014.09.098 0040-4039/© 2014 Elsevier Ltd. All rights reserved. the best of our knowledge, no reports of oxidative, $sp^3 C$ —H thiolation of ethers with sodium sulfinates are known. Herein, we have reported a novel protocol to construct unsymmetrical sulfides using sodium sulfinates as sulfur sources (Scheme 1b).

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A new method for palladium-catalyzed arylthiolation of ethers with sodium sulfinates is described. The

C-H bond in various ethers was successfully converted into C-S bond to yield the corresponding sulfides

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Inspired by our previous work,¹⁰ our initial attempt started with the reaction of sodium *p*-tolylsulfinate **1a** (1.0 mmol) and 1,4-dioxane **2a** (4 mL) catalyzed with 2.0 mol % PdCl₂ using di-*tert*-butyl peroxide (DTBP, 2.0 equiv) as the oxidant at 120 °C for 12 h (Table 1, entry 1). By GC–MS, the reaction took place with a 35% yield. Efforts were then made to get the optimized reaction conditions, the arylthiolation of 1,4-dioxane with sodium *p*-tolylsulfinate (**1a**, 1.0 mmol) was selected as the model reaction, several palladium catalysts such as Pd(OAc)₂, PdBr₂, (CH₃CN)₂PdCl₂, and (Ph₃P)₄Pd were investigated (Table 1, entries 2–5), and among them Pd(OAc)₂ (2.0 mol %) showed the best efficiency to give the corresponding



Scheme 1. Methods of C-S bond formation using sodium sulfinates.

E-mail addresses: jnxiang@hnu.edu.cn (J. Xiang), guosr9609@lsu.edu.cn (Y. Yuan).

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Table 1

Optimization of the reaction conditions^a



	DIDI (2.0)	(0113011)21 0012(2.0)	01
5	DTBP (2.0)	$(Ph_{3}P)_{4}Pd(2.0)$	56
6	DTBP (2.0)	CuBr(2.0)	N.D. ^c
7	DTBP (2.0)	Cu(OAc) ₂ (2.0)	N.D. ^c
8	DTBP (2.0)	$Fe(acac)_3(2.0)$	N.D. ^c
9	DCP (2.0)	Pd(OAc) ₂ (2.0)	70
10	TBPB (2.0)	$Pd(OAc)_2(2.0)$	61
11	TBHP (2.0)	$Pd(OAc)_2(2.0)$	51
12	CAN (2.0)	$Pd(OAc)_2(2.0)$	N.D. ^c
13	$(NH_4)_2S_2O_8$ (2.0)	Pd(OAc) ₂ (2.0)	N.D. ^c
14	$K_2S_2O_8(2.0)$	$Pd(OAc)_2(2.0)$	N.D. ^c
15	PhI(OAc) ₂ (2.0)	$Pd(OAc)_2(2.0)$	N.D. ^c
16	DDQ (2.0)	Pd(OAc) ₂ (2.0)	N.D. ^c
17	DTPB (1.0)	$Pd(OAc)_2(2.0)$	65 ^d
18	DTPB (3.0)	$Pd(OAc)_{2}(2.0)$	80 ^e
19	TBPB (2.0)	$Pd(OAc)_2(1.0)$	78
20	TBPB (2.0)	$Pd(OAc)_2(0.5)$	51

 a Reaction conditions: 1a (1.0 mmol), 2a (4 mL), heated at 120 $^\circ C$ for 12 h with 2.0 mmol % catalyst.

^bIsolated yield.

^cNot detected by GC-MS.

^dDTBP (1.0 equiv).

^eDTBP (3.0 equiv).

product **3aa** in 81% (Table 1, entry 2) yield at 120 °C under an argon atmosphere (Table 1, entries 1–5). The formation of the desired product halted with other metal catalysts, such as CuBr, Cu(OAc)₂, and FeCl₃·6H₂O (Table 1, entries 6–8). Palladium plays a pivotal role in the catalytic cycle, although the exact mechanism is unclear.

The oxidant plays another important role in the activation of the inactive C-H bond. The reaction is less efficient and proceeds with only a moderate yield when other oxidants were used such as tert-butyl hydroperoxide (TBHP), dicumyl peroxide (DCP) and tert-butyl perbenzoate (TBPB). DTBP proved to be the best oxidant (Table 1, entries 9–11). Under the present reaction conditions, other organic and inorganic oxidants, such as ceric ammonium nitrate (CAN), (NH₄)₂S₂O₈, K₂S₂O₈, PhI(OAc)₂, and DDQ were also examined and were found to impede the transformation (Table 1, entries 12-16). The appropriate amount of DTBP was 2.0 equiv and no significant increased yield of 3aa was observed with less or more than 2.0 equiv of DTBP (Table 1, entries 17 and 18). It is worth noting that a similar yield could still be achieved when the amount of the catalyst loading was decreased to 1 mol% (Table 1, entry 19). Further reduction of the catalyst loading to 0.5 mol % reduced the reaction yield (Table 1, entry 20).

Under optimized reaction conditions $(2 \text{ mol }\% \text{ of } Pd(OAc)_2$, 2 equiv of DTBP, 4 mL of 1,4-dioxane, 120 °C, 12 h), the scope of the Pd-catalyzed direct arylthiolation using sodium sulfinates as arylthiolation reagents was investigated. As can be seen from Table 2, the reactions of a wide range of sodium arenesulfinates with 1,4-dioxane generate the desired arylthiolated products in moderate to good yields. The substituted sodium arenesulfinates with electron-donating groups, such as methyl and methoxy reacted with dioxane efficiently and afforded the corresponding

Table 2

Thiolation of 1,4-dioxane with sodium sulfinates^{a,b}



^a Reaction condition: **1** (1.0 mmol), **2a** (4.0 mL), DTBP (2.0 mmol), Pd(OAc)₂ (2 mol %) heated at 120 °C for 12 h.

^b Isolated yield based on **1**.

products **3aa–3ac** in 72–81% yields (Table 2, entries 1–3). The reaction is also tolerant of electron-withdrawing substituents such as chlorine, bromine, and trifluoromethyl groups on the aromatic ring of sodium arenesulfinates and the products **3ad**, **3ae**, and **3ef** were observed in 73%, 77%, and 79% yields, respectively (Table 2, entries 4–6). The more bulky 2-naphthalenesulfinic acid sodium salt was a good substrate for this thiolation reaction as shown for the successful formation of **3ag** in 72% yield (Table 2, entry 7). It is worth noting that this protocol is also applicable to heterocyclic aromatics such as thiophene with 59% yield (Table 2, entry 8). However,

Table 3

Thiolation of ethers with sodium arenesulfinates^{a,b}



 a Reaction condition: 1 (1.0 mmol), 2a (4.0 mL), DTBP (2.0 mmol), Pd(OAc)_2 (2 mol %) heated at 120 °C for 12 h. b Isolated yield based on 1.

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when sodium arenesulfinate containing-nitro groups were used as a substrate, no desired crosscoupling products were observed. This reaction was not sensitive to steric hindrance (Table 2, entries 9–12), for example, when sodium arenesulfinate bearing an *ortho*-substituent (sodium 2-methylbenzenesulfinate, **1j**) was treated with 1,4-dioxane, and the desired product **3aj** was obtained with 73% yield.

Subsequently, the scope of ethers in the present reaction was also examined (Table 3). A variety of ethers including cyclic and unsymmetrical linear ethers could couple with different sodium arenesulfinates. Tetrahydrofuran (THF) was found to work effectively with different kinds of sodium arenesulfinates and the corresponding products were obtained in moderate yields (entries 1–9). The electronic effects of the substituents on the aromatic ring of sodium arenesulfinate did not substantially influence the reaction reactivity, as both electron-rich and electron-deficient sodium arenesulfinates worked. ortho-substituted sodium arenesulfinate was tolerated, but the steric effects of the sodium arenesulfinate did impact on the yields (entries 8 and 9). For example, the reaction of sodium 2-chloro benzenesulfinate with THF proceeded only with 51% yield (entry 9). In addition, compared to the yield of 1,4-dioxane, one can conclude that the activity of THF is poorer than 1,4dioxane, which maybe influenced by the number of oxygen atoms and the size of the cyclic ester. In the case of methyl tert-butyl ether (MTBE), which has one CH_3 group adjacent to the oxygen atom and a sterically large group, the reaction proceeded with poor yields (entries 10-12). Clearly, the sterically demanding tert-butyl had an effect on the reaction. 1,2-dimethoxyethane (DME) furnished a mixture of products with moderate yields, it's very interesting that the main thiolation reaction took place on the terminal methyl group not the methylene (entry 13–15).

Lastly, under optimal reaction conditions, the applicability of this method to sulfonyl chlorides with 1,4-dioxane was tested (Table 4). This procedure was found to be similarly compatible with a broad range of substrates. Notably, substrates bearing both electron-withdrawing and electron-donating groups were all successfully tolerated in this reaction. However, the yields were lower than those of sodium arenesulfinate. Unfortunately, similar to sodium 4-nitrobenzenesulfinate, 4-nitrobenzenesulfonyl chloride also failed to deliver the products.

Table 4



^a Reaction conditions: sulfonyl chlorides (1.0 mmol), **2a** (4 mL), heated at 120 °C for 12 h with 2.0 mmol % catalyst.
^bIsolated vield.



Scheme 2. Reaction of sodium arenesulfinates with 1,4-dioxane catalyzed by $Pd(OAc)_2$ without DTBP.



Scheme 3. Reaction of disulfide with 1,4-dioxane only using DTBP as oxidant with 2 mmol % Pd(OAc)₂.



Scheme 4. Plausible reaction mechanism.

To investigate the possible mechanism for this arylthiolation, a series of experiments were carried out. The disulfide was the major product when the model reaction was carried out with only using 10 mol % Pd(OAc)₂ catalyst without DTBP (Scheme 2). The intermediate product of disulfide could react with dioxane smoothly under the same conditions (Scheme 3). In a subsequent reaction, the formation of the desired product **3aa** was suppressed by addition of TEMPO as a radial inhibitor, thus revealing that the mechanism proceeds via a radical process.^{8–10}

As far as sodium aryl sulfinates are concerned, a plausible mechanism is illustrated in Scheme 3. Similar to the metal-catalyzed thiolation reaction of arenesulfonyl chlorides or sulfonyl hydrazides, the plausible mechanism involves the following several steps: (I) sodium aryl sulfonate is converted into the disulfide by Pd(OAc)₂; (II) the *tert*-butoxyl radical, which is formed by the decomposition of DTBP under heat, can abstract hydrogen from the ether to generate the corresponding alkyl radical intermediate; (III) the radical intermediate reacts with disulfide affording the product and ArS⁻ free radical which is trapped by another alkyl radical (see Scheme 4).

In conclusion, we have developed an efficient Pd-catalyzed arylthiolation using sodium sulfinates as sulfur sources. In the presence of 2.0 mol % of Pd(OAc)₂ and DTBP as an oxidant, a broad range of sodium sulfinates react with ethers smoothly giving arylthiol substituted ethers in moderate to good yields. This finding offers a new, simple, and mild method for the synthesis of aryl alkyl sulfides. 4

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Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 21276068) and the Normal Foundation of Zhejiang Education Department (No. Y201329988).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.09. 098.

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